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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. resume	John Chabot (partial) (1 page)	02/05/2001	b(6)

COLLECTION:
Federal Records
White House Commission on Complementary and Alternative Medicine Policy [WHCCAMP]

OA/Box Number: 43232

FOLDER TITLE:
WHCCAM Commissioner Binder, Day 3, May 16, 2001 [1]

2011-0568-S
kc812

RESTRICTION CODES

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

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b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
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Divider Title: Research Methodology

Questions for the Research Methodology Panel:

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

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

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

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

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

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

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

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

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

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Chabot

Divider Title: _____

John Chabot, M.D.
Columbia University

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[001]

Curriculum Vitae

Date of Prepared: February 5, 2001

Personal Data:

Name: John A. Chabot, M.D.

(b)(6)

Citizenship: United States

Address: (b)(6)
Rye, New York 10580

Academic Training

College: Tufts University
Medford, Massachusetts
BS in Engineering Science
1975 - 1979

Medical School: Doctor of Medicine
Dartmouth Medical School
Hanover, New Hampshire
1979 1983

Student Fellow in Pathology
Mary Hitchcock Memorial Hospital
Hanover, New Hampshire
1980-1982

Licensure: New York #166730 1
DEA #BC2270041

Training:

Internship, Residency, and Fellowship in Transplantation:
Columbia-Presbyterian Medical Center, New York
1983 - 1990

Military Service: None

Board Certification: American Board of Surgery
June, 1991

#31

Professional Organizations and Societies:

American Medical Association
Fellow in the American College of Surgeons
New York Surgical Society
New York Transplantation Society
American Association of Endocrine Surgeons

Academic Appointments:

1990 -1991	Instructor in Clinical Surgery College of Physicians and Surgeons Columbia University
1991- 1998	Assistant Professor of Surgery College of Physicians & Surgeons Columbia University, New York
1998 – Present	Associate Professor of Clinical Surgery College of Physicians & Surgeons Columbia University, New York

Hospital Appointments:

1990-1991	Assistant in Surgery Presbyterian Hospital New York, New York
1991-1998	Assistant Attending Presbyterian Hospital New York, New York
1998-Present	Associate Attending The New York-Presbyterian Hospital New York, New York 1998 - Present

Positions Held:

1990-1992	Assistant Program Director, Surgical Residency
1991-1996	Thyroid Clinic, Surgical Chief
1992-1996	Associate Program Director, Surgical Residency
1995-1997	Director, Surgical Intensive Care
7/1/95-6/30/98	Voting Member-Faculty Council of the Faculty of Medicine
1995 Present	Chief of Hepatobiliary & Pancreatic Surgery
11/96-Present	Vice Chairman, Department of Surgery Columbia University, College of Physicians & Surgeons
11/99-Present	Medical Director of Operating Rooms Columbia Presbyterian Campus of New York Presbyterian Hospital
1999-Present	Faculty Practice Organization – Board of Governors

Honors:

1978	Magna Cum Laude, Tufts University
1978	Tau Beta Pi, National Engineering Honor Society
1979	Sigma XI, Scientific Research Society
1979	Alpha Omega Alpha, Dartmouth Medical School
1980	1985-87 Irvington House Institute Fellowship
1987	Upjohn Young Scientist Award
1987-88	Blakemore Prize for Surgical Research
1990	Blakemore Award for Surgical Research
1990	Ortho Foundation Award
1992	Habif Scholar
1998	Thomas C. King Resident Teaching Award

Professional Development:

Completed Post-Graduate Course #4, "Ultrasound for Surgeons" October 23, 2000 - 2000 Annual Clinical Congress of the American College of Surgeons, Chicago, Illinois

Committees:

1993-2000	Oncology Protocol Review Committee Columbia Presbyterian Medical Center; Comprehensive Cancer Center
1995, July	OR and Anesthesia Committee
1995 Present	Emergency Services Committee of the Medical Board
11/96-11/97	President - Presbyterian Hospital-Alumni Society
1996-Present	Clinical Operations Council, Presbyterian Hospital
1996-Present	Oncology Protocol Review
1997-1997	Executive Reengineering Steering Committee, Presbyterian Hospital
1997-1998	Chairman - Oncology Protocol Review Committee Columbia Presbyterian Medical Center; Comprehensive Cancer Center
4/99-Present	Chairman – Invasive Procedures Committee

Teaching at College of Physicians & Surgeons:

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

Publications – Original:

1. **Chabot JA**, Riback P, Cochrane DE. Elevated cyclic AMP levels fail to inhibit extracellular calcium dependent histamine secretion from rat mast cells. Life Sciences 28:1155-62, 1980

2. Colacchio T, **Chabot JA**, Zimmerman B. Differential mucin staining in colorectal neoplasms. Am. J. Surg. 147:666-669, 1984

3. **Chabot JA**, Colacchio T. Early colonic dysplasia: comparison of differential mucin and 3H thymidine labeling. Am. J. Surg. 147:666-669, 19984

4. Weber CJ, Hardy MA, Rivera S, Bailey-Braxton D, Michler R, Thomas W, **Chabot JA**, Pi-Sunyer X, Wood M, Reemstsma K. Diabetic mouse bioassay for functional and immunologic human and primate islet zerograft survival. Transpl. Proc. 18, 823-830, 1986.

5. Hardy MA, Lau HT, Liu X, **Chabot JA**, Mg A. Cytolytic lymphocytes against pancreatic islet cells in diabetic BB rats. Transpl. Proc. 18:1523-24, 1986

6. **Chabot JA**, Lau HT, Reemtsma K, Hardy MA. Long term survival of islet allografts in spontaneously diabetic BB rats without chronic immunosuppression Transpl. Proc. 18, 510-530, 19986

7. Sadeghi AM, Weber C, **Chabot JA**, Kurlandsky PA, Michler R, Rose ER, Reemtsma K, Smith CR. Hemorrhagic pancreatitis following heart-lung preservation in primates. Surg.. Forum 37:257-258, 1986

8. **Chabot JA**, Lau HT, Reemtsma K, Hardy MA. Successful islet transplantation in BB rats without chronic immunosuppression. Transpl. Proc. 19-974-975, 1987

9. **Chabot JA**, Weber CJ, Hardy MA, Rivera S, Bailey-Braxton D, Strausberg L, Wood M, Chow J, Reemtsma K. Synergy of ALS and UVB in prolongation of primate to mouse islet zenograft and survival. Transpl. Proc. 19: 1160-1165, 1987.

10. Oluwole FS, **Chabot JA**, Pepino P, Reemtsma K, Hardy MA. In vistro mechanism responsible for prolonged rat cardiac allograft survival induced by ultraviolet-irradiated donor-specific blood and cyclosporine. Transpl. Proc. 19:4331-4333, 1987

11. Oluwole SF, **Chabot JA**, Pepino P, Reemtsma K, Hardy MA. In vitro immune responsiveness in rats transfused with UV irradiated donor specific blood. Transpl. Proc. 20:131-133, 1988

12. Pepino P, Fawwaz R, **Chabot JA**, Oluwole SF, Reemtsma K, Hardy MA. Subcutaneous administration of donor lymphocytes and Tc 99M-MAA to achieve specific immunosuppression. Surg. Forum 37:361-366, 1987

13. Pepino P, **Chabot JA**, Tannenbaum G, Oluwole SF, Fawwaz R, Reemtsma K, Hardy MA. Effect of carbodiimide on donor-specific blood transfusion in rats. Transplantation 45:6690, 1988

14. Oluwole SF, **Chabot JA**, Pepino P, Reemtsma K, Hardy MA. Mechanism of immunological unresponsiveness induced by UV-irradiated donor specific blood transfusion and peri-transplant cyclosporine. Transplantation 46:352-358, 1988

15. Stegall MD, **Chabot JA**, Weber C, Reemtsma K, Hardy, MA. Pancreatic islet allo and Xenotransplantation in Cynomolgus monkeys and the effect of cyclosporine on glucose tolerance. Surg. Forum 39:384-396, 1989

16. Pepino P, Hardy MA, **Chabot JA**, Berger C, Morboe CC, Gutierrez C, Wasfie T. UVB-irradiated allogenic bone marrow transplantation in rats: Prevention of graft versus host disease without immunosuppression. Transpl. Proc. 21:442, 1989

17. **Chabot JA**, Stegall MD, Weber C, Reemtsma K, Hardy MA. Pancreatic islet allo- and Xenotransplantation in Cynomolgus monkeys Transpl. Proc. 21:2739-2740, 1989

18. Stegall MD, **Chabot JA**, Norton J, Engelstad K, Hin M, Hardy MA. The effect of cyclosporine on glucose tolerance in Cynomolgus monkeys. Transpl. Proc. 21:2995-2996, 1989

19. Stegall MD, **Chabot JA**, Weber C, Reemtsma K, Hardy MA. Pancreatic islet transplantation in Cynomolgus monkeys. Transplantation 48: 944-950, 1989

20. **Chabot JA**, Pepino P, Wasfie T, Stegall MD, Marboe C, Hardy MA UVB pretreatment of rat bone marrow allografts: Prevention of GVHD and the induction of allochimerism and donor-specific unresponsiveness. Transplantation 49:886-889, 1990

21. Stegall MD, **Chabot JA**, Tezuka K, Reemtsma K, hardy MA. The importance of donor MHC compatibility in the allo and autoimmune destruction of islet grafts in the BB rat. Transpl. Proc. 22 (4):2011-2012, 1990

22. Wasfie T, **Chabot JA**, Pepino P, Tezuka KI, hardy MA. UVB irradiated bone marrow allografts in rats: induction of unresponsiveness for long-term heart allografts without GVHD. Transpl. Proc. 22(4):2011-2012, 1990

23. LoGerfo P, **Chabot JA**, Gazetas P. The intraoperative incidence of detectable bilateral and multicentric disease in papillary cancer of the thyroid. Surgery 108(6):958-62, 1990

24. Gundlach M, Wasfie T, DiAgaati V, **Chabot JA**, Oluwole S, Hardy MA. The role of passenger leukocytes in the immunogenicity of intestinal and cardiac allografts in the rat. Transpl. Proc. 23 (1)187-188, 1991

25. **Chabot JA**, The role of passenger leukocytes in the immunogenicity of intestinal and cardiac allografts in the rat. Transplant Proc. 24(3):1131-1132, 1992

26. Zarkin BA, **Chabot JA**, LoGerfo P. Solitary Thyroid Nodules (letter;comment). New England Journal of Medicine 328(8): 553-559, 1993

27. Koa J, Houck K, Fan Y, Haehnel I, Libutti SK, Hayton ML, Grikscheit T, **Chabot JA**, Nowygrod R, Greenberg S, Kuang WJ, Leung D, Hayward IR, Kisiel W. Heath M, Brett J, Stern DM. Characterization of a Novel Tumor-Derived Cytokine. The Journal of Biological Chemistry Vol. 269(40):25106-25119, 1994

28. LoGerfo P, Ditkoff BE, **Chabot JA**, Feind CR. Thyroid Surgery using Monitored Anesthesia Care: An Alternative to General Anesthesia., Thyroid 4(4), 437-3439, Winter, 1994

29. Ditkoff BA, **Chabot JA**, LoGerfo P, Jin S, Feind CR. Hurthle Cell Cancer of the Thyroid: The Incidence of Multifocal and Bilateral Disease. Thyroidology: Clinical and Experimental,7(2) 49-54, January 1995

30. Greenfeld JI, **Chabot JA**, Oluwole SF, Hardy MA. The Mechanism of UVB Prevention of Graft Versus Host Disease. J. Surg. Rec. 60(1):137-41, Jan.1996

31. Marvin MR, Libutti SK, Kayton M, Kao J, Hayward J, Grikscheit T, Yan Fan AB, Brett J, Weinberg A, Nowygrod R, LoGerfo P, Feind CR, Hansen KS, Schwarz M, Stern D, **Chabot JA**. A Novel Tumor-Derived Mediator That Sensitizes Cytokine-Resistant Tumors to Tumor Necrosis Factor. Journal of Surgical Research Vol. 63(1) 248-255, June 1996

32. Ditkoff BA, Marvin M, Yemul S, Shi Y, **Chabot JA**, Feind CR, LoGerfo P. Detection of Circulating Thyroid Cells in Peripheral Blood Surgery 120(6):959-964, December 1966 - Presented at the American Ass. of Endocrine Surgeons, Napa Valley, California, April 21-23, 1996.

33. Ditkoff BA, Marvin MR, Brichkow I, Yemul S, **Chabot JA**, Feind CR, LoGerfo P. The Detection of Circulating Thyroid cells in the Peripheral Bloodstream: Preoperative and Postoperative Analysis Thyroidology: Clinical and Experimental:8;87-94. 1996

34. Ditkoff BS, **Chabot J**, Feind CR, LoGerfo P. Parathyroid Surgery using Monitored Anesthesia Care As An Alternative to General Anesthesia. American Journal of Surgery 172(6):698-703, Dec. 1996

35. Hagopian EJ, **Chabot JA**, Oluwole SF, Benvenisty AI, Hardy MA. Allograft Rejection and Corticosteroids in Acute Pancreatitis Following Renal and Cardiac Transplantation. Transplantation Proceedings 29(1-2):583, Feb.-March 1997

36. Marvin MR, Kayton ML, O'Toole KM, Rowe DH, DeRosa C, Kindred A, Trokhan S, **Chabot JA**, Kandel J. A Metastasizing Model of Anaplastic Human Wilms Tumor in the Nude Mouse European Journal of Pediatric Surgery 8(5):295-8, October 1998

37. Marvin MR, Southhall JC, Trokhan S, DeRosa C, **Chabot JA**. Liver Metastases are Enhanced in Homozygous Deletionally Mutant ICAM-1 or LFA-1 Mice. Journal of Surgical Research 80(2):143-8, December 1998

38. Khan ZR, Neugut AI, Ahsan H, **Chabot JA**. Risk Factors for Biliary Tract Cancers. American Journal of Gastroenterology 94(1):149-52, January 1999

39. Mongero LB, Beck JR, Kroslowitz RM, Argenziano M, **Chabot JA**. Treatment of Primary Peritoneal Mesothelioma by Hyperthemic Intraperitoneal Chemotherapy. Perfusion 14(2):141-5, March 1999

40. Schwarz MA, Kandel J, Brett J, Li J, Hayward J, Schwarz RE, Chappey O, Wautier JL, **Chabot JA**, LoGerfo P, Stern D. Endothelial-monocyte Activating Polypeptide II, a Novel Antitumor Cytokine that Suppresses Primary and Metastatic Tumor Growth and Induces Apoptosis in Growing Endothelial Cells. Journal of Experimental Medicine190(3):341-54, August 2, 1999

41. Horvath KD, **Chabot JA**. An Aggressive Resectional Approach to Cystic Neoplasms of the Pancreas. American Journal of Surgery 178(4):269-74, October 1999

Case Reports:

1. Flores RM, Goldstein DJ, Sung RS, Steinglass K, Weinstein S, **Chabot JA**. Transthoracic Transdiaphragmatic Excision of Simultaneous Lung and Adrenal Lesions. Annals of Thoracic Surgery 65(3), 833-5, March 1998

2. Marvin MR, Lefkowitch J, Ishak KG, **Chabot JA**. Long-term Survival of a Young Woman with Peripheral Cholangiocarcinoma; A Case Report. Journal of Clinical Gastroenterology 28(1):64-6, January 1999

Reviews, Chapters and Editorials:

1. Hardy MA, **Chabot JA,** Tannenbaum G, Lau HT. Immunomodulation by ultraviolet irradiation. Prog. Clin. Biol. Res. 224:119-138, 1986

2. Hardy MA, **Chabot JA,** Tannenbaum G, Benvenisty AI. Graft acceptance; modification of immunogenisity of the donor or the donor organ with or without host immunosuppression. In Small Bowel Transplantation, Experimental and Clinical Fundamentals (Ed. Hammelman and Deltz) Springer-Verlag. 1987

3. Tanuenbaum G, Benvenisty AI, **Chabot JA,** Hardy MA. Stoma or no stoma in intestinal transplantation. In Small Bowel Tranplantation, Experimental and Clinical Fundamentals (Ed. Hammelman and Deltz) Springer-Verlag. 1987

4. Reemtsma K, **Chabot JA,** Pi-Sunyer FX, Weber C. Isolation of zenogenic islets of langerhans for human transplantation; comparative studies of primate, human, Marine and rabbit islets. Proc. International Symposium on Artificial Organs, Biomedical Engineering and Transplantation. VCH Publishers, 1987

5. Hardy, MA, **Chabot JA.** Alteration of pancreatic islet immunogenicity using ultraviolet irradiation; synergism with peritransplant immunosuppression. In Transplantation of the Endocrine Pancreas eds. Van Schilfgaarde, R and Hardy MA. Elsevier Press VII:301-307, 1988

6. Perosa F, Hardy MA, Guarini L, **Chabot JA,** Dammacco F, Ferrone S. Anti-idiotypic monoclonal antibodies to anti-HLA class II monoclonal antibodies. Potential applications in the treatment of autoimmune diseases. In Recent Advances in Autoimmunity and Tumor Immunology ed Dammacco F, 1990

7. King TC, **Chabot JA,** Geller PG. Surgery Pretest: Self-Assessment and Review. McGraw-Hill Inc. 1992

8. **Chabot JA,** Altman RP. Thyroid and Parathyroid. Pediatric Surgery W. B. Saunders, 1993

9. **Chabot, JA.** The Whipple Procedure – 1935 to 1993. P&S Review, 1993

10. Neugut A, Marvin MR, Pella, V, **Chabot JA.** An Overview of Adenocarcinoma of the Small Intestine Oncology (Huntington)11(4):529 550, April 1997

Abstracts:

1. Ration of Protein Kinase A I to Protein Kinase A II in Human Thyroid Cancer. Zarkin BS, Xu DB, Obici S, **Chabot JA**. The Association for Academic Surgery, Hershey, Pennsylvania, November 10-13, 1993

2. Ratio of Protein Kinases A I to Protein Kinase A II in Human. Zarkin BS, D-B Xu, Obici S, **Chabot JA,** Thyroid Cancer Assoc. for Academic Surg. Hershey, Pennsylvania November 10-13, 1993

3. Zarkin BE, **Chabot JA**, LoGerfo P. Letter to the Editor Solitary Thyroid Nodule NEJM 329(5):360 New England Journal of Medicine 1993

4. Libutti SK, Bessler M, **Chabot JA**, Bass LS, Kirsch AJ, Oz MC, Auteri JS, Treat MR, Nowygrod R. Reinforcement of high-risk anastomosis using laser-activated protein solders; a clinical study. Low-Power Laser Applications for Laser-Tissue Fusion. White JV, White PA, Bass LS, Editors Proc. SPIE876, 1993

5. Endoscopic Ultrasound in Patients with Suspected Common Bile Duct Stones Before Laparoscopic Cholecystectomy Stevens, PD, Lightdale CJ, **Chabot JA**, Green PHR, Stein JA, Siegel LM, Abedi M, Garcia-Carrasquillo RJ. Departments of Medicine & Surgery, Columbia University, College of Physicians and Surgeons, New York Submitted to: 10th International Symposium of Endoscopic Ultrasonography, Cleveland, Ohio October, 1995

6. Preoperative vs Postoperative ERCP for Suspected Choledocholithiasis in Patients Undergoing Laparoscopic Cholecystectomy;A Randomized Trial. Stevens PD, Green PHR, Stein JA, Lightdale CJ, **Chabot JA,** LoGerfo P, Abedi J, Garcia-Carrasquillo RJ, Siegel LM, Abo SR, Rubin M, Lewis SK, Lin D, Diamond B. Gastrointestinal Endoscopy 41, 417, 1995

7. Acute Pancreatitis in the Transplant Population. Stevens PD, Micale P, Finegold J, Pollach E, Chin S, Lightdale DC, Green PHR, **Chabot JA,** Siegel L. Gastroenterology 108, A393 1995

8. Acute Pancreatitis in the Transplant Population Stevens PD, Finegold J, Micale P, Lightdale CJ, Green PHR, **Chabot JA,** Siegel L. Am. J. Gastroenterology A2416157, 1995

9. Preoperative vs Postoperative ERCP for Suspected Common Duct Stones in Patients Undergoing Laparoscopic Cholecystectomy; A Randomized Trial. Stevens PD, Green PHR, Stein JA, Lightdale CJ, **Chabot JA,** LoGerfo P, Abedi M, Garcia-Carrasquillo RJ, Siegel LH. Am. J. Gastroenterology A248, 1615 1995

10. Endoscopic Ultrasound in Patients with Suspected Common Bile Duct Stones Before Laparoscopic Cholecystectomy. Stevens PD, Lightdale CJ, **Chabot JA,** Green PHR, Stein JA, Siegel LH, Abedi M. Garcia-Carrasquillo RJ. Gastrointest Endoscopy 43, 2, A13, 852 1996

11. ERCP Before or After Laparoscopic Cholecystectomy ? Final Results From a Randomized Trial; Length of Stay Differences. Stevens, PD, VandeMierop F, Green PHR, **Chabot JA,** Stein JA, Garcia-Carrasquillo RJ, Diamond B, Lightdale CJ. Gastroenterology, 110-A477 1996

12. ERCP Before or After Laparoscopic Cholecystectomy ? Final Results of a Randomized Trial; Analysis of Negative Outcomes Van deMierop F, Stevens PD, Green PHR, **Chabot JA,** Stein JA, Garcia-Carrasquillo RJ, Lightdale CJ. Gastroenterology 110,A479 1996

13. ERCP Before or After Laparoscopic Cholecystectomy ? Final Results of Randomized Trial; Long Term Follow-up Van deMierop F, Stevens PD, Garcia-Carrasquillo RJ, Schmulewitz N, Green PHR, Stein JA, **Chabot JA,** Lightdale CJ. Gastroenterology 110,A480 1996

14. Implementation of a Standardized Multi-Disciplinary Treatment Protocol for Acute GI Hemorrhage Finegold J, Garcia-Carrasquillo RJ, Stevens PD, Van deMierop F, Green PHR, Battagliano M, Meyer F, Rosenberg R, Lewis SK, Rubin M, **Chabot JA,** Diamond B, Lightdale CJ. Gastrointestinal Endoscopy 43,356 1996

15. Mortality, Morbidity and Cost-Related Outcomes in Acute Pancreatitis; A Prospective Study Finegold J, Stevens PD, Huynh J, Jenders RA, Diamond B, Poneros J, Slotweiner P, **Chabot JA,** Green PHR, Lightdale CJ. Gastroenterology 112:A15 1997

In Press:

Stevens PD, **Chabot JA,** VandeMeirop F, Green PHR, Stein JA, Garcia-Carrasquillo RJ, Siegel LM, Diamond BD, Lightdale CJ. Endoscopic Retrograde Cholaniopancreatography Before or After Laparoscopic Cholecystectomy? A Randomized Trial. American Journal of Gastroenterology

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

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

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

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

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

Thus far, I have made three observations:

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

From: "Pollen, Geraldine (NCCAM)" <polleng@od.nih.gov>
To: "'jac4@columbia.edu'" <jac4@columbia.edu>
Subject: White House Commission
Date: Fri, 20 Apr 2001 14:09:01 -0400
Status: O

Dear Dr. Chabot:

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

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

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

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

Please let me know if you have any questions.

We are looking forward to your participation in this meeting.

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

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

Qualitative Research

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

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

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

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

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

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

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

What policy recommendations you offer regarding re rch on CAM practices and procedures for the (lon's consideration as it develops its report to the President and Congress?

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Divider Title: Angell

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

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

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

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

Angell

RESEARCH METHODOLOGY IN CAM

by Marcia Angell, M. D.

CAM is an umbrella term for a large number of disparate practices based on different theories. These include, for example, homeopathy, therapeutic touch, naturopathy, chiropractic, acupuncture, herbal medicine, imagery, crystal healing, and chelation therapy. They have very little in common except for the fact that they are practiced largely in the absence of good scientific evidence to support their use.

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

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

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

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

In summary, there are not two kinds of medicine -- CAM and standard medicine. There is only medicine that has been adequately tested, and medicine that hasn't. In general, CAM falls into the second category. Standard medicine falls into both. Whether biologically implausible (or even impossible) remedies should be tested is arguable. I have come to believe that widely used remedies should be tested for safety and effectiveness, even when they are biologically implausible. If they are shown to be effective and reasonably safe, they should be incorporated into clinical practice, regardless of whether they originated as CAM. But there are no short-cuts, and there should be no free passes.

"Medicine that works..."

but what about ~~if~~ ~~it~~ medicine "that works" to kill a targeted tumor, and yet also causes ~~unbearable, and other~~ negative physical as well as ~~psy~~ emotional effects? If the ~~person~~ ~~them~~ cancer is eliminated but the person's spirit is

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Jacobs

Divider Title: _____

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

Jennifer Jacobs, MD, MPH, is a family practice physician specializing in homeopathic medicine in Edmonds, Washington. She received her MD degree from Wayne State University in Detroit, Michigan and a Masters in Public Health at the University of Washington in Seattle. She is the President of the American Institute of Homeopathy and founded the special interest group of the American Public Health Association on Complementary and Alternative Health Practices. She is also clinical assistant professor of Epidemiology at the University of Washington School of Public Health and Community Medicine, where she conducts research on the use of homeopathic medicines in primary care. She was a member of the program advisory council of the NIH Office of Alternative Medicine from 1992 through 1996. Her publication (May, 1994) in the journal *Pediatrics*, "Treatment of Acute Childhood Diarrhea with Homeopathic Medicine: A Randomized Clinical Trial in Nicaragua," was the first study of homeopathic medicine to be published in a mainstream peer-review medical journal in the United States. She has co-authored a book, *Healing with Homeopathy*, published by Warner Books.

Research Methodology and Homeopathic Medicine

Jennifer Jacobs, MD, MPH, Clinical Assistant Professor, Epidemiology, University of Washington, Seattle, President, American Institute of Homeopathy

Overview of Homeopathy

Homeopathy has long been an enigma to modern medical scientists, due largely to the high dilutions of the medicines used. While the mechanism of action of homeopathy remains unknown, nearly 200 years of anecdotal evidence from all parts of the world has convinced many patients, as well as physicians, of its efficacy. In France, 33% of medical doctors use it in their practices, while in India it is used by up to half of the population. In the US, 3.4 percent of the population used homeopathy in 1997, a 500% increase from 1990.

Homeopathy is based on the "principle of similars", first described by Samuel Hahnemann in the late 18th century. Substances that have been found to cause certain symptoms when given to healthy subjects, are used to treat those same symptoms in someone who is sick. Homeopathic remedies are prepared using a series of 1:10 or 1:100 dilutions of an initial substance that is vigorously shaken between each step. This process, called potentization, is thought to release the inherent dynamic energy of the substance, which then stimulates the self-healing mechanism of the body. Another important tenet of homeopathy is individualization, whereby each person is treated with a specific remedy, which fits his or her unique pattern of physical, emotional, and mental symptoms. For this reason, different people with the same diagnosis may receive one of several different homeopathic remedies.

Homeopathic research

Homeopathy has been found to be extremely safe, due to the low concentrations of active substances used, as well as efficacious in many clinical trials. A meta-analysis published in *The Lancet* in 1997 established clearly the efficacy of homeopathy when compared to placebo. The other finding of this study, however, was that few of these trials had been replicated by independent investigators. Since that time some studies have been replicated and there is now adequate evidence to justify its use in several conditions.

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

Barriers to Homeopathic Research

It is clear that more high quality research needs to be done in homeopathy, especially in the area of replication of previous studies. However, there are many barriers both political and methodological, to carrying out good homeopathic research. Many of these also apply to other areas of complementary and alternative medicine research (CAM).

1. Funding and sample size. Funding has been limited by the fact that homeopathic medicines are generic and cannot be patented, thus there are no huge profits to be made from investments in research. Because of this, sample sizes have been relatively small in homeopathic trials, which means that only large differences can be detected between treatment groups. In my childhood diarrhea research, p-values in the range of 0.03 to 0.05 were found in the individual studies of 87-125 subjects, but when these studies are combined to yield more than 200 cases, the p-value drops to 0.002. If enough money is available for enough subjects, even small differences in effect size can be found to be statistically significant, as is the case for many highly marketed allopathic drugs.

2. Individualization. Unlike other CAM modalities, homeopathy lends itself well to conventional randomized placebo-control trial (RCT) methodology, the gold standard for medical research. This is because homeopathic medicines are prescribed on sugar pills. However, the individualized nature of homeopathic practice makes a strict application of RCT methodology difficult. Unlike trials in conventional medicine, all patients with the same illness are not prescribed the same medicine in homeopathy. Several strategies have been used to incorporate individualization into the RCT study design. These include individualizing the treatment each subject receives and comparing the outcome of the homeopathic group as a whole to placebo, limiting study subjects only to those who fit a specific homeopathic remedy picture, and using homeopathic combination remedies that contain the most common medicines for a specific illness.

3. Outcome Measures. It is important that outcome measures used in clinical research of homeopathy and other CAM modalities reflect the holistic nature of these practices. In conventional medical research, often only one or two specific parameters are evaluated, such as a blood test or blood pressure measurement, which do not reflect the response of the patient as a whole to treatment. This can be solved by using already existing symptom scores for various illnesses, such as the Kupperman Menopausal Index for hot flashes. More globally, quality of life indicators, such as the SF-36 Health Survey, can be used to evaluate subjective feelings as well as limitations of work and social activities and general health status. Other outcomes, such as days of

If we can reference these stats, they are good for report/ Congress briefing

missed school or work, the cost of medical care, and patient satisfaction, are also important in evaluating the results of CAM treatment modalities.

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

5. Effectiveness and Longitudinal Studies. Once the efficacy of homeopathy is established firmly, the use of placebo can be eliminated, by randomizing subjects to receive either conventional medical care or homeopathy. This would give a more accurate representation of what homeopathy has to offer in actual clinical practice, rather than the artificial situation created by a RCT. Longitudinal studies of homeopathic patients over several years should document the preventative as well as curative aspects of this modality. Cost analyses of such trials also would be useful, to evaluate the impact of the use of homeopathy in the health care system.

Recommendations

There is now adequate evidence-based research to justify the use of homeopathy in several conditions (influenza, diarrhea, post-operative ileus, and allergies), yet the belief structures of scientists continue to block its widespread application. Many critics have stated that no matter how many clinical trials are published, they will never accept homeopathy until its mechanism of action is understood. This, in my view, is foolhardy, as there are many examples of drugs in modern medicine, aspirin for one, which were used for years before their mechanism was understood. It also is chauvinistic for us to think that at this point in time we understand everything there is to know about science.

Homeopathy does work, most likely on a subatomic or subtle energy level that has not yet been elucidated. My first recommendation to the commission is that the government establish an initiative to find out how homeopathy works. This could revolutionize our understanding of health and disease, as well as open the door to other new healing strategies.

Modern medicine is at an impasse. Four hundred twenty-five billion dollars per year are spent in the US treating the six leading illnesses and health care costs continue to rise. Drug costs now exceed $100 billion per year and are predicted to reach nearly $400 billion by 2010. Recent studies have shown that adverse reactions to allopathic drugs *taken as directed* is the fourth leading cause of death in hospitals in this country. One recent survey showed that more than half of all physicians said they would not do it again when asked about their decision to go into medicine.

} reference?

In the 1999 special issue on alternative medicine, the editors of *JAMA* wrote: "There is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data or unproven (sic) medicine, for which evidence is lacking." Homeopathy deserves the kind of careful evaluation that is necessary to establish its legitimacy. The commission should charge government agencies to thoroughly investigate homeopathy so that it can become available within the health care system to anyone who wants it. Well-funded research into clinical efficacy and cost effectiveness should demonstrate that homeopathy is a low-cost way to provide health care to a wide segment of our population. It may also make them healthier.

In closing, I would like to share the following internet news release:

China Gives Limited Approval to Western Medicine

At the conclusion of a 3-day meeting held in the Great Hall of the People in Beijing March 28-30, an elite panel of 12 Traditional Chinese Medicine (TCM) practitioners declared, "There is sufficient evidence of Western Medicine's effectiveness to expand its use into TCM and to encourage further studies of its physiology and clinical value".

"In particular", the panel's report stated, "Western Medicine shows promise as adjunctive treatment to TCM. As a stand-alone medicine, however, its efficacy is mainly in the areas of acute and catastrophic care that comprise a relatively minor percentage of total patient complaints."

The consensus report was particularly critical of biomedical research design, since the panel had based their assessments solely on data from randomized controlled trials. Key points of the critique were:

1. Biomedical trials are designed to determine the mean response to treatment. This outcome is of limited value to TCM practitioners who are trained to devise individualized treatment protocols.
2. Biomedical trials test one drug at a time. This approach is bound to reveal unwanted side effects. In contrast, TCM seeks combinations of herbs to balance out adverse effects of individual herbs.
3. Diseases chosen for study in biomedical research are, too often, imprecise collections of symptoms, such as Irritable Bowel Syndrome or Chronic Fatigue Syndrome. These categorizations lump together different conditions that are readily distinguishable by TCM diagnosis.

"It is also our impression", the report continued, "that Western Medicine is based in a belief system that is powerfully reinforced by the large sums of money patients and insurance companies are willing to pay for treatment."

"We strongly recommend", the panel concluded, "that patients should be treated with Western Medicine only on a referral basis from a practitioner of TCM".

Clinical Research in Homeopathy- selected References

Gibson RG, Gibson SL, MacNeill AD, Buchanan WW. Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial. *Br J Clin Pharmacol* 1980; 9:453-9.

Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homoeopathy a placebo response? Controlled trial of homoeopathic potency, with pollen in hayfever as model. *Lancet* 1986; ii:881-5.

Fisher P, Greenwood A, Huskisson EC, Turner P, Belon P. Effect of homeopathic treatment on fibrositis (primary fibromyalgia). *Br Med J* 1989;299:365-6.

Ferley JP, Smirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homeopathic preparation in the treatment of influenza-like syndromes. *Br J Clin Pharmacol* 1989;27:329-35.

Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. *Brit Med J* 1991;302:316-23.

Jacobs J, Jiminez LM, Gloyd S, Gale J, Crothers D. Treatment of acute childhood diarrhea with homeopathic medicine: a randomized clinical trial in Nicaragua, *Pediatrics* 1994; 93: 719-25.

Reilly D, Taylor MA, Beattie NGM, et al. Is evidence for homoeopathy reproducible? *Lancet* 1994;344: 1601-6.

Lökken P, Straumsheim PA, Tveiten D, Skjelbred P, Borchgrevink CF. Effect of homoeopathy on pain and other events after acute trauma: placebo controlled trial with bilateral oral surgery. *Brit Med J* 1995; 310:1439-42.

de Lange de Klerk ESM, Blommers J, Kuik DJ, Bezemer PD, Feenstra L. Effect of homoeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections. *Brit Med J* 1994; 309:1329-32

Linde, Clausius N, Ramirez G, et. al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet 1997;* 350:834-43.

Jacobs J, Chapman EH, Crothers D. Patient characteristics and practice patterns of physicians using homeopathy. *Arch Fam Med.* 1998; 7:537-40.

Weiser M, Strosser W, Klein P. Homeopathic vs conventional treatment of vertigo: a randomized double-blind controlled clinical study. *Arch Otolaryngol Head Neck Surg.* 1998; 124:879-85.

Chapman EH, Weintraub RJ, Milburn MA, Pirozzi TO, Woo E. Homeopathic treatment of mild traumatic brain injury: A randomized, double-blind, placebo-controlled trial. *J Head Trauma R* 1999; 521-42.

Jacobs J, Jimenez LM, Malthouse S, et. al. Homeopathic treatment of acute childhood diarrhea: results from a clinical trial in Nepal. *J Altern Complem Med* 2000; 6:131-9.

Barnett ED, Levatin JL, Chapman EH, et. al Challenges of evaluating homeopathic treatment of acute otitis media. *Pediatr Infect Dis J.* 2000; 19:273-5.

Taylor, MA, Reilly D, Llewellyn-Jones RH, McSharry C, Aitchison TC. Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *BMJ* 2000; 321:471-6.

Jacobs, J, Springer DS, Crothers D. Homeopathic treatment of acute otitis media in children: a preliminary randomized controlled trial. *Pediatr Infect Dis J* 2001; 20:177-83.

Jennifer Jacobs, MD, MPH, is a family practice physician specializing in homeopathic medicine in Edmonds, Washington. She received her MD degree from Wayne State University in Detroit, Michigan and a Masters in Public Health at the University of Washington in Seattle. She is the President of the American Institute of Homeopathy and founded the special interest group of the American Public Health Association on Complementary and Alternative Health Practices. She is also clinical assistant professor of Epidemiology at the University of Washington School of Public Health and Community Medicine, where she conducts research on the use of homeopathic medicines in primary care. She was a member of the program advisory council of the NIH Office of Alternative Medicine from 1992 through 1996. Her publication (May, 1994) in the journal *Pediatrics*, "Treatment of Acute Childhood Diarrhea with Homeopathic Medicine: A Randomized Clinical Trial in Nicaragua," was the first study of homeopathic medicine to be published in a mainstream peer-review medical journal in the United States. She has co-authored a book, *Healing with Homeopathy*, published by Warner Books.

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White

Divider Title: _____

B. Alex White, DDS, DrPH

Dr. White is a senior investigator and assistant program director for the Economic, Social, and Health Services Research Program at Kaiser Permanente's Center for Health Research (CHR) in Portland, Oregon. He is responsible for leading a research program using the 185,000-member dental plan of Kaiser Permanente, Northwest Division, as a laboratory. His interests include oral health outcomes, treatment effectiveness, practice variation, and cost-effectiveness analysis of dental programs and treatments. In addition, he is interested in the association between oral health and general health. He is currently principal investigator for the Oregon Center for Complementary and Alternative Medicine, a five-year, $8 million grant that is evaluating complementary and alternative approaches for craniofacial disorders. Prior to joining the CHR, Dr. White held appointments at the National Institute of Dental Research, the Health Care Financing Administration, the Agency for Health Care Policy and Research, and the White House.

Dr. White received a B.A. in 1979 and a Doctor of Dental Surgery degree in 1983 from the University of North Carolina at Chapel Hill. From 1983 to 1985, he completed a two-year general practice residency in dentistry at the Brigham and Women's Hospital in Boston, Massachusetts. He received an MPH degree and an MS degree in 1987 from the Harvard University School of Public Health. From 1987 to 1989, he was a Robert Wood Johnson Dental Services Research Fellow at the Harvard School of Dental Medicine. In 1992, he received a Doctor of Public Health degree from the Harvard School of Public Health. He has academic appointments at the University of California, San Francisco,

School of Dentistry; the University of North Carolina School of Dentistry; the Oregon Health Sciences University Schools of Medicine and Dentistry; and the University of Washington School of Dentistry.

Dr. White is past president of the American Association of Public Health Dentistry and the Behavioral Sciences and Health Services Research Group, International Association for Dental Research. He is Director-Elect of the American Board of Dental Public Health and a fellow in the American College of Dentists. He serves as co-chair of the National Affairs Committee of the American Association for Dental Research. Dr. White is also secretary-treasurer of the Multnomah Dental Society.

White House Commission on Complementary and Alternative Medicine
The Challenges of CAM Research and Research Training:
Research Methodology

Testimony

B. Alex White, DDS, DrPH

Principal Investigator
Oregon Center for Complementary and Alternative Medicine
and

Senior Investigator and Assistant Program Director
Economic, Social, and Health Services Research

Center for Health Research
Kaiser Permanente Northwest
Portland, Oregon

May 16, 2001

Recommendations on Policy from the Oregon Center for Complementary and Alternative Medicine:

- In general, the evidence base for CAM is less well developed than for most other areas of therapeutic practice. Continued research support is imperative at all levels—biomedical, clinical, behavioral, and health services—to continue to develop the evidence base for CAM.

- The objective of any policy recommendation should be to ensure the best science possible, with appropriate methods and recognizing the importance of the cultural context in which the CAM therapy is usually provided and in which it is being studied.

- Research support should focus on three broad areas: research on specific CAM therapies for particular diseases or conditions; development of research methods to better understand CAM therapies and associated outcomes; and support for infrastructure to conduct CAM research, including education and training of new CAM researchers.

- The NCCAM should continue as the focal point for CAM research support. Partnerships between NCCAM and other federal agencies— including other NIH institutes, the Agency for Healthcare Research and Quality, Health Resources and Services Administration, and the Health Care Financing Administration, and Centers for Disease Control and Prevention—and with other non-federal agencies should be encouraged.

- Development of measurement instruments of psychosocial characteristics and quality of life (QOL), including qualitative methods, is needed in order to better specify characteristics of patients and practitioners, patient-practitioner interactions, and non-traditional outcomes;

- Biomarkers of intervention effects and essential to understand the mechanisms and biological effect of CAM therapies, especially whole body effects such as immunological and humoral

markers, and effects related to subtle energies such as electromagnetic fields and brain function.

- Knowledge of whole complex therapeutic systems is central to CAM research, to address such issues as maintaining fidelity to the medical systems they represent, the development of individualized protocols, and standardization of system-specific diagnoses These are critical to ensure appropriate application of research methods and interpretation of results.

- Additional research is crucial to further understand the statistical and quantitative aspects of design, including the statistical implications of modifications to standard RCT design, analysis of trials with complex interventions, and measurement of subtle effects.

- Research is essential into the cultural context in which CAM therapies are provided and in which it is being studies and into the adoption and integration of CAM therapies into conventional medical care and health plans.

- Additional health services research is needed in CAM to understand how these therapies are used and their impact on costs and outcomes. Such studies should include explicit cost-benefit and cost-effectiveness analyses where appropriate.

Oregon Center for Complementary and Alternative Medicine: Context and Experience

The Oregon Center for Complementary and Alternative Medicine[1] (OCCAM) at Kaiser Permanente's Center for Health Research (CHR) in Portland, Oregon, is unique in bringing together four major training and education institutions for complementary and alternative medicine (CAM), as well as a major academic school of dentistry and its clinical research center, and a large operating health maintenance organization (HMO) with a well-established prepaid group practice dental care plan of 185,000 members, in itself unique in the nation. OCCAM is exceptionally fortunate in its complement of researchers and practitioners in Traditional Chinese Medicine, chiropractic, therapeutic massage, naturopathy, medicine, and dentistry, as well as in key disciplines—anthropology, biostatistics, economics, clinical psychology, genetics, among others—required to carry out public-domain, academic-quality research in one of the oldest health and dental services research centers in the United States.

Since the early seventies, the CHR has been centrally active in conducting numerous national clinical trials, serving as both clinical centers and coordinating centers, sponsored by various institutes of NIH. It has also conducted a broad range of other research as well, under the auspices of the CDC, Health Care Financing Administration, Agency for Health Care Quality, and others. The CHR's long-standing research agenda in non-drug and lifestyle approaches to health promotion and disease prevention made CAM research a natural progression; in the late nineties, the CHR enlisted the Pacific Northwest's CAM training institutions as colleagues and collaborators in forming a research program.

By now, OCCAM's institutions, researchers, and practitioners have enjoyed almost four years of invaluable experience in conducting CAM research through forging, first, a successful center proposal (the first effort commenced in 1998), and then an infrastructure and agenda for OCCAM's research in targeted craniofacial disorders. Under the leadership of the CHR investigators, OCCAM has undertaken Phase II trials in CAM diagnosis, management, and therapies in selected facial and jaw (craniofacial) disorders, and is preparing for Phase III trials.

[1] For a more detailed description of the institutions that collaborate in OCCAM, its administrative structure and projects, see the short appendix at the end of this paper.

OCCAM's Phase II trials include rigorous evaluation of the potential efficacy, acceptability, resource use effects, patient satisfaction, compliance, adherence, response to symptoms, and psychosocial and other health outcomes associated with CAM practices as well as the physiological and psychological mechanisms underlying some of these practices.

OCCAM Perspective

The perspective that underpins OCCAM is that the methods of science—careful and clearly documented observation, rigorous empiricism, and well-conceived experimental studies, including appropriate double-blind, placebo-controlled randomized clinical trials—are fully applicable across the range of new possibilities and old traditions available for study in craniofacial disorders.

CAM research, as defined by the National Center for Complementary and Alternative Medicine (NCCAM), "covers a broad range of healing philosophies, approaches, and therapies. It generally is defined as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies." It includes the 70-90% of human health care that is not delivered by conventional, biomedically oriented practitioners. This includes health care practices used instead of biomedicine (alternative), as well as therapies that are used in addition to biomedicine (complementary).

This definition includes three components: (1) health care taking place as self-care: utilizing drugs, compounds, and practices available without recourse to a practitioner; (2) community-based health care: utilizing resources available in the community but from non-professional sources; and (3) professionalized health care: utilizing trained practitioners from systems other than the biomedical establishment. In OCCAM, we are interested primarily in the third component of CAM and focus our research efforts there. The network and collaboration of Portland CAM professionals, including contractual arrangements with the four CAM institutions, provide a unique opportunity to study multiple CAM approaches with teaching/practicing experts in each of the fields.

Research and Research Methods in CAM

At the outset, consideration of methodological issues in CAM clinical research must acknowledge that CAM comprises a considerable variety of techniques, modalities, and systems that offer a broad range of challenges for research design. Many of the healing systems that comprise the current CAM spectrum—Traditional Chinese Medicine and acupuncture, naturopathic medicine, chiropractic, massage therapy, various energy medicines including healing touch, native American healing systems, Ayurvedic medicine—believe both that treatment should be individualized to the patient and that the effects of single aspects of the treatment cannot be conceptuality or meaningfully separated out for analysis. In some cases, "individualized treatment" means treatment prescribed according to the CAM diagnosis rather than the allopathic diagnosis, certainly a reasonable view. In other cases, "individualized treatment" goes further, viewing every patient as unique and proscribing similar treatments across patients. Both of these positions pose challenges for standard clinical trials design, in regard to standardized diagnostic procedures, reliable and valid measurement of relevant baseline patient characteristics, and standardization of treatment approaches so that patients would be treated the same regardless of practitioner. Further, some CAM interventions seek changes in patient attitudes or experiences that have not been typically measured by questionnaires, such as feelings of wholeness, centeredness, enhanced energy levels, heightened awareness, or clear mind. New assessment tools may be required to identify outcomes that are meaningful to the CAM systems. These issues overlap and interact with the myriad aspects of meaning often glossed as the placebo effect.

Earlier efforts in developing CAM research methods

The Office of Alternative Medicine (OAM) shortly after its founding in 1991 recognized the need to examine research methods in relation to CAM. Two methods conferences resulted, one in Chantilly, Virginia, in 1992, and one in Bethesda, Maryland, in 1995. Cassileth *et al.* (1995), reporting on the Chantilly conference, provided a thoughtful and comprehensive review of the challenges. While leaning in favor of randomized clinical trials (RCTs) whenever feasible, they recognized that RCTs are not always possible, even in conventional medical research. The report

recognized that cultural biases against CAM threatened equitable funding for CAM projects, and often invoked requirements for CAM studies that exceeded those for any existing conventional medical field. A blanket recommendation was that CAM researchers should search the literature to learn how the problems they encounter have been handled successfully by clever and innovative modifications of standard designs. To this end, the report further recommended regular NIH-sponsored conferences with published proceedings.

Levin *et al.* (1997), reporting from the Bethesda conference, asserted that CAM modalities do not offer any truly unique methodological challenges, and that the existing methods are well-equipped for use on any novel medical therapies. This report recognized no less than seven categories of CAM features that were claimed to make conventional research difficult: (1) complex individualized interventions, (2) individualization of therapeutic effects, (3) focalized effects versus systematic perturbations, (4) systemic correspondences and correlations, (5) long-term effects, (6) reconceptualization of the human body, and (7) multifactorial etiology. Rather than dealing with all seven, the report synthesized them into two: (1) multiplicity (how to deal with interventions whose component parts might vary across patients for reasons inherent in the CAM approach), and (2) *worldview* (how to study effects when the CAM approach's basic mechanisms and measurements violate current scientific consensus). One of the most remarkable conclusions of this group was that a battery of named statistical methods were adequate to handle the challenges of CAM research, when most (if not all) of those methods find virtually no use in conventional medical research. which could scarcely be regarded as a standard tool. To claim that methods <u>not</u> used in conventional medical research are sufficient to handle the putative uniqueness of CAM modalities is, of course, quite different from saying that CAM can be evaluated by the methods of conventional medical research, the ostensible conclusion of the Levin article.

A contemporaneous report from the same conference (Vickers *et al.* 1997) took a broader view, citing the need to be humble in light of our ignorance of the ultimate workings of the world. We should focus on basics, such as *What is a good research question?* and *How can we match our questions with good designs?* A good question is one that is answerable, and this is more likely if it is explicit, focused, and practical. A good question is also important, meaning that it will

is this true? or self-limiting....

lead to the alleviation or prevention of human suffering. With respect to methods, however, this panel pinned most of its hopes on the RCT. The intellectual rationale for this was that (1) cause precedes effect, (2) mental beliefs do not influence chance events, and (3) the beliefs of the researcher do not have unmediated physical effects. What is remarkable here is that none of these are the classical justifications for a RCT. What is important here is that *concurrent controls* are indeed an essential feature of CAM intervention studies.

Most writers on CAM research methods have arrived at the same comforting conclusion, that current methods are essentially adequate. Jonas (1997) was sanguine that existing methods can and should be applied, with the interesting argument that at least some CAM investigations might lead us to look at phenomena that are outside currently accepted scientific knowledge (such as effects of intention, or subtle transmission of molecular level information), and it is indeed difficult to imagine how science could pursue those areas without some motivation, such as CAM practices that are based on them. In relating the British experience, which is rather longer than the American, Vickers (1996) also strongly supported the use of conventional methods, with examples in which a problem claimed by CAM proponents to rule out an RCT was in fact part of a conventional RCT that succeeded. He further coined the term *pragmatic trial* to refer to an absence of interference with the usual behavior of the practitioner. He does not consider that pragmatic trials easily lead to comparing whole medicines (such as Traditional Chinese Medicine vs. naturopathy), an enterprise that seems unlikely to succeed when there is little or no incentive for either type of alternative practitioner to participate in a study in which they stand to lose so much. Among the fundamental advice that Vickers gave to CAM researchers was to "keep it simple," and indeed the notion of "large, simple trials" has had some favorable opinion. He does not, however, worry that reducing a complex treatment to a simple one for the purpose of testing may be putting the evaluation cart before the therapeutic horse.

The Journal of the American Medical Association chose 1998 as the year to feature CAM research in its affiliated journals (Fontanarosa 2000). Of the 74 articles, only two were plausibly about methodology. One of those (Ezzo, Berman, Vickers 2000) cited 30 CAM areas in which reviews were completed or ongoing. The point was made that despite the general methodological deficiencies in the CAM research literature, if one looked at the medical

literature broadly, they could easily find areas in which research methods were no better than in CAM research.

While many CAM methodologic challenges can be met by adapting existing designs developed for biomedical clinical research, others are likely to require more novel approaches. For example, randomized, placebo-controlled clinical trials have been performed on such diverse CAM therapies as single herbs (Hirata *et al.* 1997, Marks *et al.* 2000), herbal formulas (Bensoussan *et al.* 1998, Weber *et al.* 1999), reflexology (Oleson *et al.* 1993), magnet therapy (Vallbona *et al.* 1997, Collacott *et al.* 2000) and acupuncture (Lao *et al.* 1999, Kleinhenz *et al.* 1999). In the latter case, where existing research designs are in need of expansion, protocols are being considered that reflect individualized diagnoses and treatment (Bensoussan *et al.* 1998; Gao *et al.* 1999), compensate when practitioner blinding is not feasible (Caspi *et al.* 2000), assess the importance of patient choice (Thomas *et al.* 1999), and examine *systems* of health care rather than their component parts (Lao *et al.* 2000).

In the most recent opinion about CAM research methods, Nahin and Strauss (2001) recognize a gradation of studies, from comparisons of herbs (which have many similarities to standard drug trials), through trials comparing different versions of a CAM modality (which are like comparisons of similar medical procedures), to phenomenological studies of CAM modalities as whole entities, without trying to dissect out the operative features (like comparisons of medical with surgical therapies). They call this last group "pragmatic trials" because they allow the practitioners to do what they believe best rather than forcing them to follow an externally dictated protocol. Note, however, that the implied method of comparison here is still a basic, parallel, two-group design. What Nahin and Strauss do not explore is whether the patient-tailored elements of a complex trial can, in fact, be analyzed, and we will argue in the next section that such methods have been developed, but are not being used.

Consider the various ways in which CAM and conventional approaches clash. What do we do when there is a difference in the way they diagnose the disease? Which is "right," what disease are we actually treating, and what do we do with the patients diagnosed differently under the two systems? What do we do when the CAM modality claims that it needs to resolve a prior

underlying problem before attacking the problem identified in the trial, and how do we take this into account in our analysis? Classical RCTs generally specify fairly rigid treatment protocols for the condition under study, but CAM modalities allow for an elaborate interaction between the patient and the practitioner, and the alternative practitioners believe that this interaction is fundamental to their medicine. Is it possible that we can actually negate the beneficial effects of an alternative therapy by coercing it into an allopathic mold for the purpose of evaluation? Conventional methods answer the question "which treatment produces more successes" but the clinically relevant question to the patient with the disease is "what are the probabilities that I will do better under this or that choice of therapy," a question that goes unanswered in conventional medical research. RCTs seem to address the question of which method should be universally advocated, whereas the CAM question seems to be "which patients would benefit from which modality or system." Conversely, RCTs form a class of designs, rather than one single design. They have modifiable features that can be adapted to specific scientific problems. CAM researchers clearly need to take into account how RCTs can be used to test their approaches, just as conventional researchers have slowly and sometimes grudgingly learned.

Moving CAM into Clinical Practice: How do health plans adopt new technologies?

Our model of CAM integration conceptualizes CAM and conventional care as a family of health care technologies. Often, an HMO will perform a technology assessment to determine when, if ever, a technology should be covered. Technology assessment has been defined as "the evaluation of the safety, effectiveness, and appropriateness of the many devices, medical and surgical procedures, and pharmaceuticals promoted to improve a patient's condition or quality of life" (Matuszkewski 1997). It usually involves critical evaluation and synthesis of evidence available from clinical studies and other systematic evidence, often incorporating expert opinion. It may be formal, involving various staff and committees, or informal, performed entirely by the HMO medical director, for example.

When deciding on which new technologies to adopt, HMOs consider the benefits and costs of adoption. To maximize social benefit, HMOs ideally would adopt only such technologies with medical benefits that exceed societal costs of development and use. However, such HMO

decisions are usually made within a competitive environment that constrains consideration of social costs or benefits that HMOs do not experience directly.

In such an environment, HMOs influence technology adoption (TA) by performing two broad functions. First, along with payers, they determine the contractual framework of the organization, delivery, and financing of care. Second, they determine the scope of adoption through various activities, including provider contracting, coverage policy development, and payment or reimbursement procedures such as practice guidelines, pre-authorization, and other forms of utilization review (Garber *et al.* 2000, Ramsey & Pauly 1997).

A technology eligible for payment or reimbursement must not be excluded in the negotiated contracts between purchasers and an HMO. This often means that the covered technology contributes to a broad service category such as inpatient or outpatient care. Typically, it should also be "medically necessary" (represent the standard of care) within the context of a particular case, and not be "experimental" or "investigational." Many contracts exclude or limit coverage for particular services with varying degrees of specificity (*e.g.*, cosmetic surgery or infertility treatment). Within the contractual framework, medical utilization review staff interpret contracts to make coverage and payment decisions.

At Kaiser Permanente, for example, an Interregional New Technology Committee (INTC) of physicians and non-physicians managers and staff makes recommendations on the medical appropriateness of new technologies to Regional Divisional Benefits Committees, Regional New Technology Committees, and local executive leadership who actually make coverage decisions. A medically appropriate technology produces expected benefits that are clinically significant and which exceed health risks by a sufficiently wide margin that the technology is worthwhile and superior to others, including none (Braslow *et al.* 1998). If a technology is chosen for coverage, patient-selection criteria are often developed to guide providers on medically necessary use and eligibility of particular patients.

Do these integration models apply to CAM?

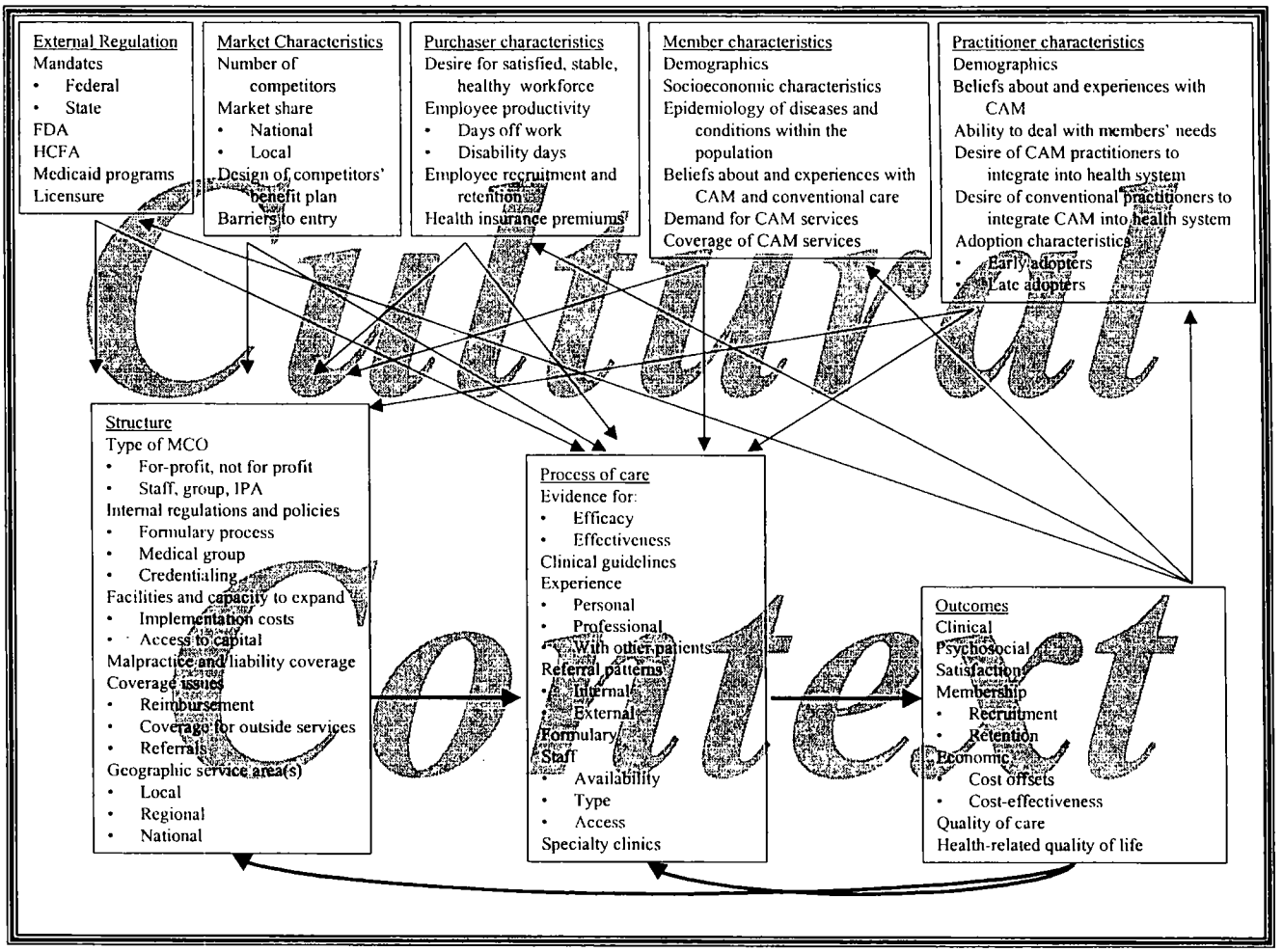
Although HMO personnel claim that technology assessment data are the most important factor in adopting technology, other factors beyond HMO control play a role: coverage and payment policies of public insurance programs such as Medicare and Medicaid, preferences of private payers (reflected in negotiated contracts), government mandates, licensing policies, litigation exposure, government support for medical research and technology assessment, producer behavior, publicity about and controversy surrounding procedures or medical devices, patient and physician demand, and market competition. As one example, decisionmakers in KPNW consider 11 different criteria in reviewing on regarding coverage decisions, only one of which is clinical efficacy.

Many of the same factors important in adopting conventional technologies are also important for CAM integration. Pelletier *et al.* (1997) reported that the need for more research of efficacy was only one of several obstacles to incorporating CAM into mainstream health care. Many relate to the factors above, including economics, ignorance about CAM, practitioner competition and division, and needs for standards of practice and licensing. In a later article, Pelletier *et al.* (1999) noted demand from consumers and purchasers appeared to be the most important factor among those influencing the decision to offer CAM, such as market research and the health plans' interest in attracting new enrollees and retaining existing enrollees.

A Model for Evaluating CAM Integration

Based on our knowledge of how HMOs consider new technologies for integration, of obstacles to integration, and of factors most influential in the decision to offer CAM, we have proposed the following model for CAM integration (Figure 1). We define integration as the coordination of CAM and conventional practice into a health care process within a health care delivery system. Our premise is that the success of CAM depends on multiple factors that may differentially impact integration. It is important to note that we do not consider the common practice of offering CAM therapies through "carveouts" granted to CAM practitioner networks to represent true integration of benefits or care in either the clinical, administrative, or financial sense.

Figure 1. A model for studying CAM integration within a health plan.



generally accepted as meeting the standard of care. Plans may create a troublesome legal double standard by requiring solid clinical evidence for new allopathic procedures such as autologous bone marrow transplantation, while covering CAM therapies without such evidence.

Process of care includes what happens to the member during the course of therapy. Whenever possible, processes of care should be based on the best scientific evidence available, including efficacy and effectiveness data (Fontanarosa & Lundberg 1998). Many HMOs have developed or adopted clinical guidelines for practitioners to manage certain conditions. In the absence of or with limited valid scientific evidence, practitioners' experience becomes a critical factor in guiding the care process. More general characteristics of the process of care such as greater standardization and shorter office visits also have significant influence over CAM integration in managed care. These factors are generally inconsistent with patient and practitioner interest in more individualized therapy, and may therefore act as impediments (Astin *et al.* 1998).

Outcomes are the result of the process of care and can be assigned to one of several domains or dimensions. Field and Lohr (1992) reported on the development of a set of outcomes that have been used by a number of committees of the Institute for Medicine, National Academy of Science. These seven dimensions include: (1) survival and life expectancy, (2) symptom states, (3) physiologic states, (4) physical function states, (5) emotional and cognitive states, (6) perceptions about present and future health, and (7) satisfaction with health care. We add economic outcomes to this list as an important outcome for evaluating the potential for CAM integration. The value of such a framework for CAM therapies, and its utility for assessing the long-term potential for CAM integration, is clear. CAM services that can be shown to improve outcomes along one or more of these dimensions would warrant consideration for adoption, implementation, and maintenance by health plans.

The core components of this model—structure, process, and outcomes—and their roles in CAM integration may be influenced by a number of external factors, which are shown in Figure 1. Many of these are known to influence CAM adoption, as discussed above. For example, external regulation (*e.g.*, state or Federal mandates) may require health plan reimbursement for certain CAM services. Through 1996, 41 states had mandated reimbursement for chiropractic services (Pelletier *et al.* 1997). A state's dental, medical, and other health practice acts may restrict the type of practitioner that may offer certain CAM services or may require a certain level of formal training in accredited institutions. All 50 states recognize chiropractors, physical therapists, and osteopaths as licensed practitioners; however, only 33 states similarly recognize acupuncturists,

11 recognize naturopaths, and one recognizes Traditional Chinese Medicine practitioners (Pelletier *et al.* 1999). Market characteristics may also influence CAM integration. In markets with little competition or where one health plan has a large market share, there may be fewer incentives to incorporate CAM services.

Purchaser, member, and practitioner characteristics—*e.g.*, desire for a stable workforce, demographic characteristics, or beliefs about and experiences with CAM—play a critical role in CAM integration. External pressures from these groups can have a significant impact on health plans. All of these influences occur within a cultural context, one that may facilitate or be a barrier to CAM integration.

As noted by the arrows in Figure 1, we hypothesize that external factors will influence a health plan's structure and the processes of care. Outcomes that result from the structure and process of care will be important determinants of the adoption, implementation, and maintenance (or integration) of CAM interventions and will influence purchaser, member, and practitioner beliefs about and demand for CAM services. Outcomes will also provide internal feedback for a health plan that will result in viable and sustainable CAM integration (or not).

Qualitative Methods in CAM Research

Although several important studies have documented levels of CAM use in general and specific populations (Astin 1998, Brown & Marcy 1991, Eisenberg 1998, 1993, Gast *et al.* 1997, Mouch *et al.* 1997, Murray & Shepherd 1993), descriptive information about the context of CAM use is often unelaborated in these reports. Important factors such cultural knowledge and beliefs about CAM are also left unexplored. Lay interpretations of CAM therapies are likewise largely absent from the literature.

Without a clear understanding of the cultural and social circumstances in which therapies occur, it is difficult—if not impossible—to know the proper questions to research, or the appropriate way to ask these questions. As a result, survey questions currently being used to evaluate CAM use may not capture the full spectrum of treatments used. Furthermore, how consumers reach

decisions to utilize CAM therapies and how they judge treatment efficacy have not been researched, and as a result have not be fully accounted for in standard survey research.

Cassidy (1995) highlights the need for qualitative approaches in the study of CAM, in order to shed light on the social and cultural context in which CAM is used by consumers and practiced by professionals. Existing qualitative research on health care decision-making supports the hypothesis that decisions to use treatments, as well as perceptions of efficacy, are greatly influenced by cultural knowledge and beliefs (Britten 1994, Donovan & Blake 1992, Trostle *et al.* 1983, van der Geest 1988), and warrant close examination.

Knowledge generated through qualitative research has been instrumental in the development of quantitative instruments (Morgan 1998, Parker *et al.* 1995, Vuckovic, Harris *et al.* 1997) and in the successful development and implementation of behavioral change and health promotion programs (Erwin *et al.* 1996, Kendall 1989, Nichter, Vuckovic & Parker, in press, Vuckovic and Stevens 1998, Vuckovic & Wick 2000.).

Some reviewers have expressed concerns about the validity of qualitative research, suggesting that the typically small sample sizes and interpretive approaches to analysis create bias and limit the generalizability of findings. While it is true that most qualitative studies have small samples and are locally situated, this may be seen as a strength, and not a weakness, of the method. These approaches have traditionally been used by anthropologists and sociologists to achieve comprehensive understandings of situations and cultural groups, and to generate hypotheses for testing in larger populations and different settings. Sufficiently trained researchers using standardized approaches to data collection and analysis minimize the risk of bias and ensure the credibility of research.

Qualitative methods—focus groups and in-depth interviews, for example—have played an increasing role in health services research to describe complex settings and interactions and to explore historical processes within institutions and communities (Corbin & Strauss 1988, Freidenberg *et al.* 1993, Hughes & DuMont 1993, Sofaer 1999, Glaser & Strauss 1967). Qualitative methods are designed to tap into the logic and language of members of a given group

(*e.g.*, health plan administrators, CAM practitioners, patients), encouraging participants to describe their experiences and knowledge in their own way, with their own words, rather than as a choice between pre-determined survey responses (Pope & Mays 1995). These techniques are particularly useful in clarifying the values, actions, and experiences of people in various roles (*e.g.*, patients and practitioners) (Hines 1993, Sofaer 1999). Qualitative methods are effective tools for examining social and cultural factors (such as secular trends in CAM use, economic factors, or ethnic customs) that interact with individual and organizational choice to influence outcomes (Janesick 1994, Maton 1993). In addition, qualitative methods provide important data for questionnaire development by identifying constructs of interest and response categories that are salient and face valid to participants.

For more than a decade, qualitative methods have been used in tandem with quantitative methods in mainstream scientific research to deepen understanding and refine interventions, measures, and outcomes. While qualitative research is labor- and time-intensive, it is imperative in CAM research as a complement to quantitative research in order to define outcomes and identify variations of meaning in people's understanding and responses.

Economic Evaluations of CAM Services

HMO coverage of CAM therapies is steadily growing in response to consumer demand, legislative mandates, and a commonly held belief by many insurers that CAM will be cost-saving. However, some experts argue that coverage and/or reimbursement of CAM is often limited below the appropriate level of treatment because insurers have little clinical or economic evidence that CAM therapies are actually effective, let alone cost-effective or cost-saving (Jancin 1999). It is clear that this lack of evidence contributes to efforts to minimize plan exposure to the perceived risks of CAM coverage, and impedes the real integration of CAM into managed care. Decisions about whether, and to what extent, CAM therapies should be integrated into managed care are largely resource allocation decisions. Such decisions can be made implicitly, as they frequently are, or explicitly in the sense that the costs and benefits of integration are clearly understood, and choices between treatments are made plain. Economic theory suggests that efficiency should be an important criterion of resource allocation decisions, *i.e.*, interventions

should be implemented that provide the highest "value for money" (*i.e.*, the greatest benefit for a given cost), all things equal. This efficiency criterion ensures that resources are deployed in a manner that provides the highest value to plan members.

Formal economic evaluation is intended to assess "value for money," and the most common method of evaluation is cost-effectiveness analysis (CEA). In a CEA, all treatment benefits are collapsed into a single measure (*e.g.*, quality-adjusted life years) that usually focuses on intermediate clinical or final health outcomes. This is probably unsatisfactory in evaluating CAM therapies because their beneficial outcomes likely include not only resolution of the clinical problem and its effect on quality of life, but results directly from the process of care itself. In other words, the true "value" of CAM may depend not only on direct health outcomes, but also on process attributes such as reassurance, hope, or provider empathy that have therapeutic value (Meenan *in press*).

In OCCAM's project development, we have adopted the framework of cost-benefit analysis in our evaluations of CAM integration from the economic perspective. Specifically, we have used the willingness-to-pay (WTP) methodology for the measurement of the value of CAM services to members. WTP is a method that allows consumers to assess benefits in a manner independent of a particular outcome specification. Within the WTP framework, consumers are allowed to value all aspects of care that are important to them, by placing a dollar value on the service, for example. In theory, this should lead to a more complete assessment of the value of CAM than might be obtained from CEA. The efficiency criterion suggests that services with a WTP value that exceeds the cost of implementation and operation are appropriate resource investments. Furthermore, it can be argued that the extent to which a CAM therapy is integrated into a health plan is dependent not only on its value to members (reflected in their WTP), but also on the accuracy with which that value is perceived by plan administrators, payers, and clinicians. All of these stakeholders make decisions about the coverage, access, and use of CAM, either at the membership, employee group, or patient level. These decisions influence the degree of CAM integration with other plan services. Stakeholder perceptions of members' value of CAM, and the extent to which they vary from members' "true" value, are a key to understanding the process of integration of CAM within managed care.

Collaborative Research in CAM

An important challenge in conducting CAM research is initiating and maintaining collaboration between conventional and CAM institutions, researchers, and practitioners. Without the support and input from CAM institutions and practitioners, conventionally trained researchers may fail to appreciate the complexity of the intervention and misinterpret important components of the CAM therapy. Without guidance from conventionally trained researchers, CAM practitioners may fail to incorporate rigorous study design elements, resulting in poor science and wasted resources. In partnership, however, conventional and CAM practitioners and researchers will develop better approaches to evaluate CAM therapies that incorporate appropriate study design as well as the complexity of CAM approaches.

Our experience in working with the various institutions and individuals involved in OCCAM has been positive. To achieve good professional relationships, we have worked to ensure several elements are present. First, we have secured a high level of institutional commitment. The presidents of the various CAM institutions, the dean of the OHSU School of Dentistry, and the director of the CHR have all been supportive of our work. Second, we have strived to establish trust among our partners and then agree upon common course of action. We have done this through project meetings, retreats, and in our day-to-day management of the research projects. Third, we have clearly specified our expectations and outcomes. These have generally focused on the three main research projects, but also include training and developmental project activities. Our focus on research and our value of good science has provided a framework for us that allows us to structure our discussions and resolve conflicts by continually asking ourselves *Is this good science?* We have sought to understand and be understood and to identify our own self-interests and mutual interests. We have not set out to "prove" one intervention is better than another but rather to determine which intervention(s) are most effective. Finally, we have shared the power and decision making within OCCAM through the committee structure and the development of clinical protocols.

References

Aickin M. Randomization, balance, and the validity and efficiency of design-adaptive allocation methods. *Journal of Statistical Planning and Inference* (in press).

Astin JA. Why patients use alternative medicine. *Journal of the American Medical Association* 1998;279(19):1548-1553.

Astin JA, Marie A, Pelletier KR, Hansen E, Haskell Wl. A review of the incorporation of complementary and alternative medicine by mainstream physicians. *Archives of Internal Medicine* 1998;158:2303-2310.

Bensousan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine. *Journal of the American Medical Association* 1998;280:1585-1589.

Braslow NM, Shatin D, McCarthy DB, Newcomer LN. Role of technology assessment in health benefits coverage for medical devices. *American Journal of Managed Care* 1998;4:SP139-SP150.

Britten N. Patients' ideas about medicines: A qualitative study of a general practice population. *British Journal of General Practitioners*, 1994; 44:465-468.

Brown JS and Marcy SA. The use of botanicals for health purposes by members of a prepaid health plan. *Research in Nursing & Health*, 1991; 14:339-350.

Caspi O, Millen C, Sechrest L. Integrity and research: Introducing the concept of dual blindness. How blind are double-blind trials in alternative medicine? *J Alternative and Complementary Medicine* 2000;6:493-498.

Cassidy CM. Social science theory and methods in the study of alternative and complementary medicine. *The Journal of Alternative & Complementary Medicine* 1995; 1(1):19-40.

Cassileth B, Jonas W, Cassidy CM, *et al.* Research Methodologies. In Berman BM, Larson DB (eds.) *Alternative Medicine: Expanding Medical Horizons* NIH Publication 94-0066. Washington DC: Government Printing Office, 1995.

Collacott EA, Zimmerman JT, White DW, Rindone JP. Bipolar permanent magnets for the treatment of chronic low back pain: a pilot study. *Journal of the American Medical Association* 2000;8:1322-1325.

Corbin JM and Strauss AL. *Unending Work and Care: Managing Chronic Illness at Home* San Francisco: Jossy-Bass, 1988.

Donabedian A. Evaluating the quality of medical care. *Milbank Memorial Fund Quarterly* 1966;44:166-206.

Donovan JL, Blake DR. Patient non-compliance: Deviance or reasoned decision-making. *Soc Sci Med*, 1992; 34:507-518.

Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States, 1990-1997. *Journal of the American Medical Association* 1998;280:1569-75.

Eisenberg DM, Kellsser RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med.* 1993; 328:246-52.

Erwin, D, Deloney L, Hanteng D, Erkman L. The role of the cancer registry in building outreach programs: The witness project example. *Journal of Registry Management.* May 1996; pp79-82.

Ezzo J, Berman BM, Vickers A. Complementary medicine and the Cochrane Collaboration. *Journal of the American Medical Association* 1998;280(18):1628-30.

Field M and Lohr K, eds. *Guidelines for Clinical Practice: From Development to Use* Washington, DC: National Academy Press, 1992.

Fontanarosa PB (ed.) Alternative Medicine: An Objective Assessment. *Journal of the American Medical Association*, 2000, 584-588.

Fontanarosa PB and Lundberg GD. Alternative medicine meets science. *Journal of the American Medical Association* 1998;280(18):1618-19.

Freidenberg J, Mulvihill M, Caraballo LR. From ethnography to survey: Some methodological issues in research on health seeking in East Harlem. *Human Organization* 1993; 52(2):151-161.

Gao S, Zhao D, Xie Y. A comparative study on the treatment of migraine headache with combined distant and local acupuncture points versus conventional drug therapy, *American Journal of Acupuncture* 1999;27:27-30.

Garber S, Ridgely MS, Taylor RS, Meill R. *Managed care and the evaluation and adoption of emerging medical technologies* Santa Monica, CA: RAND, 2000.

Gast J, Hanson C, Leiker JJ. University students' attitudes and use of alternative health practitioners and products. Paper presented at the American Public Health Association meeting, November 1997.

Glaser B, Strauss A. *The Discovery of Grounded Theory* Chicago: Aldine, 1967.

Hines AM. Linking qualitative and quantitative methods in cross-cultural survey research: Techniques from cognitive science. *American Journal of Community Psychology* 1993;21:729-746.

Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial, *Fertil Steril* 1997;68:981-986.

Hughes D, DuMont K. Using Focus Groups to Facilitate Culturally Anchored Research. *American Journal of Community Psychology*, 1993; 21(6):775-806.

Jancin B. Managed care plans add alternative medicine coverage. *Pediatric News* 1999;33:33.

Janesick VJ. The dance of qualitative research design: Metaphor, methodolatry, and meaning. In *Handbook of Qualitative Research* NK Denzin and YS Lincoln, eds. Thousand Oaks, CA: Sage Publications, 1994, pp 209-219.

Jonas WB. Researching alternative medicine. *Nature Medicine* Aug 1997;3(8):824-826.

Kendall C. The use and non-use of anthropology: The diarrheal disease control program in Honduras. In *Making Our Research Useful: Case Studies in the Utilization of Anthropological Knowledge.* John van Willigen, B. Rylko-Bauer, and A. McElroy, eds., pp. 283-303. Boulder, CO: Westview Press, 1989.

Kleinhenz J, Streitberger K, Windeler J, Gussbacher A, Mavridis G, Martin E Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendonitis, *Pain* 1999;83:235-241.

Lao L, Bergman S, Hamilton GR, Langenberg P, Berman B. Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial. *Arch Otolaryngol Head Neck Surg* 1999;125:567-572.

Lao L, Ezzo J, Berman B, Hammerschlag R (2000)Assessing clinical efficacy of acupuncture: Considerations for designing future acupuncture trials, In: *Clinical Acupuncture: Scientific Basis* (eds: Stux G, Hammerschlag R) Springer-Verlag, Berlin, pp. 187-210.

Levin JS, Glass TA, Kushi LH, Schuck JR, Steele L, Jonas WB. Quantitative methods in research on complementary and alternative medicine: a methodological manifesto. *Medical Care* 1997;35(11):1079-1094.

Marks LS, Partin AW, Epstein JI, Tyler VE, Simon I et al. Effects of saw Palmetto herbal blend in men with symptomatic benign prostatic hyperplasia (2000) *Journal of Urology* 2000;163:1451-1456.

Maton KI. A bridge between cultures: Linked ethnographic-empirical methodology for culture anchored research. *American Journal of Community Psychology* 1993 21(6): 747-773.

Matuszkewski KA. A primer on the assessment of medical technologies. *Pharmacy Practice Management Quarterly* January 1997:53-65.

Meenan RT. On developing appropriate economic measures of the benefits of complementary and alternative medicine. *Journal of Health Services Research & Policy* (in press).

Morgan DL, editor: *The Focus Group Guidebook.* Thousand Oaks, CA, Sage, 1998.

Mouch J, West B, Demisse K. Alternative/complementary healing practices within the primary health care domain: Prevalence and demographics in a county survey. Paper presented at the American Public Health Association meeting, November 1997.

Murray J, Shepherd S. Alternative or Additional Medicine? An Exploratory Study in General Practice. *Social Science and Medicine* 1993; 37(8):983-988.

Nahin RL, Strauss SE. Research into complementary and alternative medicine: problems and potential. *British Medical Journal* 20 Jan 2001;322:161-164.

Nichter M, Vuckovic N, Parker S. The Looking Good, Feeling Good Program: A Multi-Ethnic Intervention for Healthy Body Image, Nutrition and Physical Activity. In *Presenting Eating Disorders: A Handbook of Intervention and Special Challenges.* E Piran, MP Levine and C Steiner-Adair, eds. Philadelphia: Brunner-Mozel (in press).

Oleson T, Flocco W. Randomized controlled study of premenstrual symptoms with ear, hand and foot reflexology, *Obstet Gynecol* 1993;82:906-911.

Parker S, Nichter M, Nichter M, Vuckovic N, Sims C. Body image and weight concerns among African American and White adolescent females: Differences that make a difference. *Human Organization* 1995; 54(2): 103-114.

Pelletier KR, Marie A, Krasner M, Haskell WL. Current trends in the integration and reimbursement of complementary and alternative medicine by managed care, insurance carriers, and hospital providers. Haskell WL. Current trends in the integration and reimbursement of complementary and alternative medicine by managed care organizations (MCOs) and insurance providers: 1998 update and cohort analysis. *American Journal of Health Promotion* 1999;14(2):125-133.

Pope C, Mays N. Researching the parts other methods cannot reach: An introduction to qualitative methods in health and health services research. *British Medical Journal* 1995;311:42-45.

Ramsey SD, Pauly MV. Structural incentives and adoption of medical technologies in HMO and fee-for-service health insurance plans. *Inquiry* 1997;34:228-236.

Sacks HS, Chalmers TC, Smith H. Sensitivity and specificity of clinical trials. Randomized v historical controls. *Archives of Internal Medicine* 143(4):753-5, 1983 Apr. 1983.

Schuck JR, Chappell LT, Kindness G. Causal modeling and alternative medicine. *Alternative Therapies* 1997;3(2):40-47.

Sofaer S. Qualitative methods: What they are and why use them? *Health Services Research* 1999;34: 1101-1118.

Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clinical Pharmacology and Therapeutics* 1974;15:443-453.

Thomas KJ, Fitter M, Brazier J, MacPherson H, Campbell M et al. Longer term clinical and economic benefits of offering acupuncture to patients with chronic low-back pain assessed as suitable for primary care management, *Complement Ther Med* 1999;7:91-100.

Trostle, James A., Hauser, W.A. Susser I.S. The logic of noncompliance: Management of epilepsy from the patient's point of view. *Culture Medicine and Psychiatry* 1983; 7, 35-56, 1983.

Urbach P. The value of randomization and control in clinical trials. *Statistics in Medicine* 1993;12:1421-1431.

Vallbona C, Hazlewood CF, Jurida G. Response of pain to static magnetic fields in postpolio patients: a double-blind pilot study, *Arch Phys Med Rehabil* 1997;78:1200-1203.

Van der Geest S. Pharmaceutical anthropology: Perspectives for research and application. In: van der Geest S. & Whyte SR (eds.) *The Context of Medicines in Developing Countries*. Dordrecht: Kluwer Academic Publishers, 1988, pp. 329-366.

Vickers A. Methodological issues in complementary and alternative medicine research: a personal reflection on 10 years of debate in the United Kingdom. *Journal of Alternative and Complementary Medicine* 1996;2(4):515-524.

Vickers A, Cassileth B, Ernst E, Fisher P, Goldman P, Jonas W, Kang S-K, Lewith G, Schultz, Silagy C. How should we research unconventional therapies? A panel report from the Conference on Complementary and Alternative Medicine Research Methodology, National Institutes of Health. *International Journal of Technology Assessment in Health Care* 1997;13(1):111-121.

Vuckovic N., Harris EL, Beckett AK, Freeman C, Packer EW, Stewart B, Valanis B. Consumer and clinician opinions about genetic testing for breast cancer risk. *American Journal of Human Genetics.* 1997; 61(suppl):A193.

Vuckovic N and Stevens V. Ethnographic Contributions to Breast Cancer Prevention: The Women's Cancer Control Study. Society for Applied Anthropology, April 1998, San Juan, Puerto Rico.

Vuckovic N, Wick J. Oncology Patients' Experience with Complementary and Alternative Therapies: A Preliminary Report. *The Permanente Journal* 1999; 3(2):40-43.

Weber R et al. Randomized, placebo-controlled trial of Chinese herb therapy for HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 1999;22:56-64.

Appendix

Oregon Center for Complementary and Alternative Medicine in Craniofacial Disorders

The Oregon Center for Complementary and Alternative Medicine Research in Craniofacial Disorders (OCCAM) brings together schools of complementary and alternative medicine (CAM), schools of conventional medicine and dentistry, and an integrated medical and dental care system to conduct rigorous scientific investigation of CAM approaches to diagnosing and managing craniofacial disorders (CFD). The Center's primary theme is that craniofacial health is integral to overall health, and CAM approaches can simultaneously enhance them both. OCCAM is based at the Kaiser Permanente Center for Health Research. Funding for the five-year center grant is provided by the National Center for Complementary and Alternative Medicine (NCCAM), a component of the National Institutes of Health.

The Oregon College of Oriental Medicine (OCOM), National College of Naturopathic Medicine (NCNM), Western States Chiropractic College (WSCC), Oregon School of Massage (OSoM), Oregon Health Sciences University (OHSU) School of Dentistry and Dental Clinical Research Center, and Kaiser Permanente's Northwest Division—all of which are based in Portland—are collaborating through OCCAM to conduct research on various CAM approaches to CFD. These include the potential efficacy, acceptability, effects on health care resource use, patient satisfaction, compliance, adherence, response to symptoms, and psychosocial and other health outcomes associated with CAM practices as well as the physiological and psychological mechanisms underlying some of these practices.

OCCAM has undertaken research on CAM therapies in CFD diagnosis and management by conducting Phase II trials targeted toward chronic, painful temporomandubular joint disorder (TMD) and chronic adult periodontitis in preparation for Phase III trials. These projects include Phase II clinical trials to assess (1) complementary medicine treatments for TMD, including acupuncture, chiropractic, and massage therapies for men and women ages 18-70; (2) alternative medical system approaches—Traditional Chinese Medicine (TCM) and Naturopathic Medicine (NM)—for management of TMD among women ages 25-55 with multiple medical diagnoses; and (3) complementary NM approaches for chronic adult periodontitis. OCCAM brings together skilled and experienced researchers, practitioners, and faculty in conventional, complementary, and alternative medicine. Infrastructure support provided through OCCAM supports a critical mass of investigators in CAM CFD research that allows consideration of CAM issues in a variety of contexts (*e.g.*, clinical, epidemiological, sociological, economic) and uses a wide spectrum of methods.

OCCAM perspective

The perspective that underpins OCCAM is that the methods of science—careful and clearly documented observation, rigorous empiricism, and well-conceived experimental studies, including appropriate double-blind, placebo-controlled randomized clinical trials—are fully

applicable across the range of new possibilities and old traditions available for study in relation to CFDs.

CAM research, as defined by NCCAM, "covers a broad range of healing philosophies, approaches, and therapies. It generally is defined as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies." It includes the 70-90% of human health care that is not delivered by conventional, biomedically oriented practitioners. This includes health care practices used instead of biomedicine (alternative), as well as therapies that are used in addition to biomedicine (complementary). This definition includes three components: (1) health care taking place as self-care: utilizing drugs, compounds, and practices available without recourse to a practitioner; (2) community-based health care: utilizing resources available in the community but from non-professional sources; and (3) professionalized health care: utilizing trained practitioners from systems other than the biomedical establishment. In OCCAM, we are interested primarily in the third component of CAM and will focus our research efforts there. The network and collaboration of Portland CAM professionals, including contractual arrangements with the OCOM, NCNM, WSCC, and OSoM, provide a unique opportunity to study multiple CAM approaches with teaching/practicing experts in each of the fields.

Project Overview, Organization, and Administrative Structure

Research Setting

Figure 1. Overview of OCCAM Institutional Integration

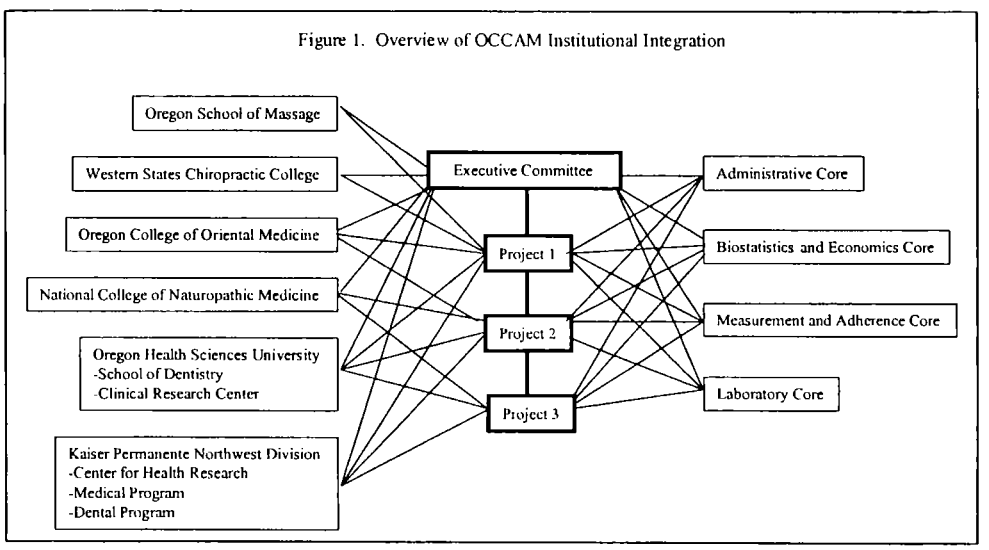


Figure 1 shows the component OCCAM institutions and their integration through its administrative, resource (biostatistics and economics, measurement and adherence, and laboratory cores), and project structure. OCCAM is based at the CHR, but is truly a collaborative effort. This effort is strengthened and enriched through various OCCAM activities (*e.g.*, Executive Committee, developmental research, research training, and community outreach). Collaboration and integration will occur largely within the activities of the three proposed research projects.

Participating Institutions

The Center for Health Research. The CHR is a professionally autonomous, multi-disciplinary research organization that conducts a program of research on medical and dental care services, organization, financing, and delivery. The Center brings experienced university- and Center-based researchers in various disciplines to a setting where extensive data are available from an operating medical and dental care system—KPNW—that encourages health services research and evaluation. Studies are directed toward the investigation of factors influencing medical care utilization, including assessment of the impact of the organization and financing of medical care on utilization patterns.

KPNW Medical and Dental Care Programs. The laboratory for OCCAM studies is Kaiser Permanente, Northwest Division. This setting gives researchers access to a comprehensive, prepaid non-profit medical care and dental care program that provides complete medical and dental services to a large, representative, general population in southwestern Washington and northwestern Oregon. The medical program in Portland was established in 1943 and now enrolls more than 432,000 members, or about 17% of the population of the Portland metropolitan area. The dental program was established in 1974 and enrolls about 187,000 participants, most of whom are also enrolled in KPNW's medical care program. The sociodemographic and characteristics of Kaiser Permanente medical and dental members correspond very closely to the metropolitan population as a whole. The membership provides a well-defined population base with known dynamic properties.

National College of Naturopathic Medicine. Founded in 1956, the NCNM is the oldest accredited naturopathic medical college in North America. NCNM is a progressive, non-profit, independent college. NCNM's educational programs are remarkably similar to the 125 allopathic, 17 osteopathic and other naturopathic medical colleges accredited in the US. NCNM grants the Doctor of Naturopathic Medicine (ND) degree and Master of Science in Oriental Medicine (MSOM) degree as approved by the State of Oregon through the Office of Degree Authorization. The College is accredited by the Council on Naturopathic Medical Education, a specialized accrediting agency recognized by the U.S. Secretary of Education.

Oregon College of Oriental Medicine. OCOM's mission is to educate and train students to become practitioners of Oriental medicine by providing high quality academic and clinical programs, and to promote and advance the knowledge and public understanding of Oriental medicine. OCOM's academic and clinical programs consist of the wide spectrum of Oriental medicine, including acupuncture, Chinese herbal medicine, Oriental physiotherapy, Qi cultivation, nutrition and exercise, as well as foundation work in Western sciences, public health, and related studies. OCOM is a non-profit 501(c)3 institution established in 1983. It currently has 28 faculty members, eight of whom are from the People's Republic of China and have extensive experience working in hospital settings.

Oregon Health Sciences University. OSHU is a century-old institution whose fundamental aim is to improve the health of all Oregonians. OHSU educates health professionals and biomedical researchers in a variety of fields, including medicine, dentistry, and nursing, and serves a yearly patient population in excess of 150,000 in its three hospitals, and dozens of medical and dental specialty clinics. In addition OHSU houses the Biomedical Information Communications Center, the Vollum Institute for Advanced Biomedical Research, the Center for Research on Occupational and Environmental Toxicology, and the Child Development and Rehabilitation Center.

OHSU School of Dentistry is a publicly supported institution established in 1898 and incorporated into OHSU in 1974; its enrollment in 1996-97 was 70 students in a variety of dentistry-related programs, including periodontology. The School encourages and supports research that adds to the knowledge of dental disease, clinical techniques, and basic oral biology as well as general basic biomedical research. Four areas of research constitute the main focus of its achievements and continued research interest: 1) *Mechanisms of Disease*,2) *Neuroscience and Temporomandibular Joint Research*, 3) *Craniofacial and Dentofacial Anomalies*, and 4) *Restorative and Implant Materials*:

OHSU General Clinical Research Center (CRC). The CRC is Oregon's premier multidisciplinary patient-oriented research facility and is part of a national network of about 75 centers, most of which are part of academic medical centers. CRC's primary mission is to provide a research infrastructure for OHSU clinical investigators and collaborators who receive their primary support from other NIH components or federal agencies. These resources include sophisticated laboratories vital for both inpatient and outpatient research, specialized research nurses, research dietitians, biostatisticians, and computer hardware and software systems, and personnel for data management and analysis.

Oregon School of Massage is a privately owned vocational school, licensed as a Career School by the State of Oregon. It was founded in Portland in 1984 by its current president and OCCAM collaborator, Ray Siderius. The Oregon Board of Massage Technicians and the Washington State Board of Massage have approved its curriculum. The curriculum includes a student clinic in which massage students perform massages for the general public. Each clinic section is limited to five students per supervisor. The school currently has a student body of about 150 students. The core faculty includes 12-20 (varies by quarter) instructors, all of whom have been approved by the Oregon Department of Education. Most of the instructors, in addition to teaching, practice privately in massage, naturopathic medicine and/or counseling. In its most widely practiced forms, massage is a general health discipline, rather than a therapeutic discipline, with most massages being performed on relatively healthy individuals. Generally, controlled research has not been done in massage environments. The most notable examples of research involving massage have been done in medical settings (*e.g.*, the Touch Research Institute at the University of Miami School of Medicine). Oregon School of Massage management and professional staffs are committed to the program and the staff development necessary to be a contributing member of the proposed study.

Western States Chiropractic College is a non-profit, 501(c)(3) institution founded in 1904, enrolling almost 500 students. WSCC offers a four-year program leading to the Doctor of Chiropractic degree and holds accreditation from the Council on Chiropractic Education and the Northwest Association of Schools and Colleges. In addition to the D.C. degree, the College grants a bachelor's degree in human biology. The College has 44 faculty and 38 part-time instructors and assistants. The curriculum emphasizes the standard basic and clinical sciences, as well as instruction in manual medicine and physical therapy.

Center Cores

The cores described here are resources that will be shared by multiple investigators and projects that will enhance research productivity and increase the functional capacity of OCCAM.

Administrative Core is responsible for OCCAM's day-to-day activities as well as program coordination and ongoing evaluation. These activities are achieved primarily through the Executive Committee; members of the Administrative Core are Executive Committee members. The Administrative Core will also be responsible for the Advisory Committee and the Career Development and Developmental Research Programs.

Biostatistics and Economics Core. The purpose of the Biostatistics and Economics Core is to manage and administer all project data, to advise on statistical aspects of design and conduct of the studies, to analyze all results in conjunction with the investigators, to facilitate access to the very considerable KNPW data resources and to provide assistance in the training of research professionals in alternative medicine. The CHR has a highly developed and experienced team of professional data managers, including programmer analysts and research analysts, who have specialized knowledge required to successfully access and manipulate these large databases.

The economics functions of the Core are closely integrated with its biostatistical functions. The Core's economics-related objectives are to develop conceptual models of complementary and alternative interventions, assess the feasibility of collecting data on economically relevant resources, costs, and outcomes, and perform economic evaluations of the specific project interventions. The economic data that are eventually collected will likely come from a variety of sources, *e.g.*, prospective tracking systems, administrative and clinical data sets, external sources, and surveys. Economic data management, study design and statistical analysis (including appropriate sample size) will combine the expertise of the economics and biostatistical components of the Core.

Measurement and Adherence Core. This core has been designed to support OCCAM projects in collecting all subject self-report data, including quality of life measures (symptom checklist, depression), and mediating variables (stress, coping, social support and social strain, dietary patterns, supplement use, physical activity, knowledge and attitudes regarding alternative medicines) for all projects and primary outcome measures for all projects.

OCCAM is focused on Phase II trials in which feasibility and acceptability of the interventions are important characteristics that need to be assessed to identify the most promising approaches for Phase III RCTs. All clinical trials require support in enhancing and monitoring adherence, since response to treatment may vary by adherence. This core will support these needs throughout the trials.

Laboratory Core. The primary function of the Core Laboratory is to provide critical laboratory services to CRC protocols and to develop laboratory technology that will provide for future utilization of the CRC resource. Historically, the CRC Core Laboratory at the OHSU has been organized to provide the highest level of professional laboratory involvement in CRC protocols and to provide significant developmental capability for bioanalytical procedures.

Over the past decade the Core Laboratory has pioneered the development of many assays at OHSU including prolactin, growth hormone, progesterone, cortisol, testosterone, melatonin and, most recently, salivary cortisol. Development of these assays by the Core Laboratory has resulted in increased utilization of both the CRC and the Core Laboratory by numerous CRC protocols that could not otherwise have been conducted.

Traditionally the core lab has performed a large portion of endocrinology related assays. As emphasis of clinical research and basic medical science research in general has shifted to more molecular, immunological and genetic based approaches, the core lab is now situated to expand into those areas.

Projects

Project 1 is evaluating complementary treatments for managing TMD pain in patients who have low-to-moderate TMD pain that does not affect their daily activities. Two hundred fifty participants aged 18-70 will be randomly assigned to receive one of three complementary treatment methods—acupuncture, chiropractic, and massage—or to receive usual care at Kaiser Permanente's TMD clinic. Changes in participants' assessment of TMD pain and symptoms as well as the feasibility and acceptability of the complementary treatments will be compared among groups.

Project 2 will evaluate alternative medicine treatments for women with TMD who have multiple health problems. One hundred fifty female participants aged 25-55 will be randomly assigned to receive one of two holistic alternative medicine treatments—Traditional Chinese Medicine or naturopathic medicine—or to receive usual care at Kaiser Permanente's TMD clinic. Practitioners in each medical discipline will diagnose participants using their own healing paradigm and will develop individualized treatments for the health problems they diagnose. Changes in participants' assessment of TMD pain and symptoms, and feasibility and acceptability of treatments will be compared among groups

Project 3 will evaluate complementary naturopathic treatments in patients who have moderate periodontal disease. Two hundred participants age 35 and over will receive a complete periodontal examination and will be randomly assigned to receive placebo, or one of three nutrient and herbal supplement treatments plus usual care (scaling and root planings). Changes in periodontal disease will be evaluated and compared among groups.

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Bruce S. Rabin

Bruce S. Rabin, M.D., Ph.D. attended medical and graduate school at the State University of New York at Buffalo. He obtained the Ph.D. in the discipline of immunology. After completing medical and graduate schooling he continued his education by doing a residency in clinical pathology.

In 1970, he joined the faculty of the Department of Pathology and the Center for Immunology at the State University of New York at Buffalo. In 1972, Dr. Rabin joined the faculty at the University of Pittsburgh Medical School and became director of the Clinical Immunopathology Laboratory.

Much of Dr. Rabin's early research at the Center for Immunology in Buffalo and the Department of Pathology in Pittsburgh involved determining how the immune system produces damage to the insulin producing g cells of the pancreas, the intestine, and the surface of the eye.

He eventually began to focus his research interest specifically on quality of health as he recognized the importance of finding ways to contribute to maintaining the health of healthy people during the aging process. One of the primary reasons that human beings become susceptible to illness is that the immune system fails to properly do its job. Thus, it was a logical step to focus upon factors that alter the function of the immune system during aging.

Dr. Rabin established a major stress and immune system research program at the Brain, Behavior, and Immunity Center, at the University of Pittsburgh Medical Center (UPMC). He has studied the effect of stress on the immune system and the pathways of communication between the brain and the immune system. His laboratory has made major contributions to understanding of how the brain and the immune system interact and influence each other's function. He has served on government panels in a variety of capacities to help promote research in mind-body interactions. In addition, he has served as the secretary/treasurer and as the President of the Psychoneuroimmunology Research Society. Currently, he is Chair of the Oversight Committee that is developing the Complementary and Integrative Medicine for the UPMC Health System. The program is called the UPMC Health Enhancement Program.

Dr. Rabin's research efforts have yielded over 300 publications to the scientific literature and his research laboratory has trained over 40 scientists. His book, Stress, Immune Function, and Health: The Connection, was published by John Wiley & Sons in February, 1999.

Draft of Comments to the White House Commission on Complementary and Alternative Medicine Policy

Bruce S. Rabin, M.D., Ph.D.
University Of Pittsburgh Medical Center Health System

May 16, 2001

I want to thank you for the opportunity to address some issues regarding Research Methodology in Complementary and Alternative Medicine. First I would like to comment on a small, uncontrolled, unscientific research effort at the University of Pittsburgh Medical Center Health System regarding terminology. As all are aware, the terms "Complementary and Alternative" and "Complementary and Integrative" have, on occasion, elicited not very subtle reactions, both pro and con, from the public and health care workers. Therefore, we conducted a consumer survey for an indication of what patients seeing physicians in our health system preferred our program to be called. As a result of this survey, we call our program the Health Enhancement Program. Our program will incorporate validated alternative approaches and conduct research studies to determine the appropriateness of modalities not yet validated.

I am a psychonueroimmunologist and I work with the mind-body connection, a subject the panel was asked to address. I will briefly comment on 3 areas of research concerns related to mind-body interactions: safety, standardization, and controls.

Safety:

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

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

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

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

Standardization:

Many arguments take place regarding the appropriateness of standardization of alternative modalities. Alternative practitioners claim their techniques cannot be standardized because different patients require adaptation of the modality to the characteristics of the particular patient. Traditional practitioners desire standardization within large scale clinical trials to determine the effectiveness of a procedure. Both approaches are correct. However, my concerns regarding standardization address the recipient of the treatment, not the treatment itself.

Applying the same modality to individuals of different personalities and emotional characteristics may yield different outcomes, as we do not know the personality characteristics of someone who is likely to experience a placebo effect? Certainly the mind-body health connection may decrease the symptoms of disease because the patient is made to feel better and tolerates their condition better. However, we also need to determine whether having an enhanced sense of well-being has an effect on the pathological basis of disease by altering the concentration of stress hormones in tissue and plasma. Cell trafficking patterns, adhesion molecule concentrations, protein synthesis, and even stem cell maturation, may be altered by effects on catecholamine and glucocorticoid plasma concentrations as a result of belief in an alternative modality a patient is experiencing. Meaningful research is not going to occur thru study of non-

standardized approaches of individual patients and anecdotal reports. Large studies of standardized approaches in well characterized patients are needed.

Some of the characteristics of subjects we are concerned about that may influence the sympathetic nervous system and hypothalamic-pituitary-adrenal axis response to alternative interventions and may contribute to understanding why the interventions work for some individuals and not others are:

Is the subject high or low in optimism, anger, hostility, a sense of humor, perceived stress, social support, religiosity or spiritualism, physical fitness?
Has the subject tried and been disappointed in traditional medical care?
Is the subject high or low in their opinion of CAM?
Does the patient have a good relationship with their physician or have they been dissatisfied with their physician?
Does the subject practice meditation or yoga?
Does the subject expect the procedure to work?

Knowing what works and in who it works is essential. Why waste time and a patient's money doing acupuncture in a patient who has characteristics that are found, thru proper research, unlikely to be associated with a therapeutic response. For example would research find that a subject who is high in hostility, low in optimism, low in expectations of a positive outcome from the procedure, sedentary, and lacks a sense of humor, be a likely responder to acupuncture.

Controls:

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

Certainly, blinding a practitioner or subject to whether or not actual massage or acupuncture were being applied is difficult. However, in the area of mind-body interventions, Institutional Review Board requirements are also a problem. For example, assume that a study is being performed of the effects of a stress coping program on the progression of MRI documented plaque size in the central nervous system of patients with multiple sclerosis. Patients are recruited to the study and sign an informed consent appropriately indicating that they will either receive the intervention or be randomized to a wait-list control group. However, the control group obviously knows that they are a control group and that, if the intervention works, they will be able to participate once the study is completed. This expectation and knowing that they are part of a study may produce a positive placebo effect. The proper control would be patients who did not know they were part of a study, believing the MRI was being done as part of routine management. However, that would be deceptive and not allowed. Thus, proper research studies of the influence of mind-body medicine on alteration of the course of disease may require modification of IRB criteria.

In conclusion:

In the absence of strong empirical data to support many CAM interventions, it is important for CAM clinics and practitioners to put a mechanism in place to systematically obtain baseline and objective outcome data on the clinical condition of the patients they treat. Subjective outcomes, without knowing that the course of a disease has been modified, will not help to end the differences between traditional and non-traditional practitioners. Detailed assessment of the patients' course of disease including changes in symptoms, objective disease measures, and laboratory parameters should be monitored and recorded in accord with guidelines that will allow the data to be published in peer-reviewed journals.

To encourage the integration of CAM delivery within the traditional medical community, each CAM clinic and practitioner should agree to either develop or participate in research protocols approved by the Institutional Review Board of their institution. CAM practitioners recruited by academic centers should be selected in part for their willingness to participate in clinical research and to have their practice subjected to scientific investigation.

CAM practices have a past, present, and future. The health care industry, the academic community, and CAM practitioners in and out of the academic world, should advocate for and pursue advances in the practice of scientific and humanistic medicine. This will occur through open communication and mutual respect. At present, the public both demands access to and frequently utilizes CAM treatments. These treatments appear

to offer something that patients want and presumably may not be receiving from "main stream" medicine. Both patients and CAM practitioners believe that the good in these treatments usually clearly outweighs their potential for harm. The challenge is therefore to offer such treatments to patients while carefully monitoring their use, subjecting CAM treatments to empirical study using accepted methods of scientific inquiry, and making every effort not to mislead patients or the public. This will only come thru collaboration and cooperation.

Thank you

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Vickers

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The Following Three Background Documents Were Submitted By Dr. Andrew Vickers, Memorial Sloan Kettering Cancer Center

Botanical Medicines for the Treatment of Cancer: Rationale, Overview of Current Data and Methodological Considerations for Phase I and II Trials

Andrew Vickers, Ph.D.
Memorial Sloan Kettering Cancer Center

Please Note:

BOTANICAL MEDICINES FOR THE TREATMENT OF CANCER: RATIONALE, OVERVIEW OF CURRENT DATA AND METHODOLOGICAL CONSIDERATIONS FOR PHASE I AND II TRIALS

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INTRODUCTION

There appears to be exceptional and growing public enthusiasm for botanical, or "herbal", medicines. In 1997, about one in eight US citizens consumed a botanical, a six-fold increase from 1990. Total expenditure was estimated at $5 billion[1]. Botanical medicine use appears particularly prevalent amongst cancer patients. In a survey of over 1000 Canadian women with breast cancer, one-quarter had used a botanical medicine and 6% had visited a botanical medicine practitioner [2]. Similar prevalence rates have been reported in surveys of 500 cancer patients at MD Anderson [3] and 46 patients undergoing radiation therapy for prostate cancer [4].

The degree of public interest in this area can also be seen on the internet, where a large number of sites market of botanicals to cancer patients or provide information and advice. A search of "Google" in April 2001 for the word "cancer" with either "herb", "herbs", "herbal" or "botanical" retrieved over 300,000 websites.

In recent years, enthusiasm for botanicals amongst cancer patients has begun to be matched by increasing scientific attention. Botanicals are being researched at major conventional cancer research institutions such as the University of California at San Francisco, Memorial Sloan-Kettering Cancer Center and MD Anderson. The *Journal of Clinical Oncology* has recently published two clinical trials of botanicals [5], [6]. At the time of writing, the National Institutes of Health is preparing a "request-for-applications" for Phase I and Phase II trials of botanicals for cancer through the recently established National Center for Complementary and Alternative Medicine [7].

In this paper I will describe the rationale for scientific investigation of botanical anticancer medicine. I will review current evidence for anticancer properties of botanical medicines, discuss some of the difficulties of botanical research and identify methodological challenges of early phase trials. Throughout this paper I will use the term "botanical medicine" to refer to extracts of plants or fungi that contain several chemical constituents.

THE SCIENTIFIC RATIONALE FOR STUDYING ANTICANCER BOTANICALS

The traditional approach: botanicals as a source of cytotoxic compounds

Many chemotherapeutic agents in contemporary clinical use were derived from natural products, predominantly from plants. One authority estimates that approximately two-thirds of anticancer drugs approved worldwide up to 1994 were derived from plant sources [8].Well-known examples include irinotecan (from *Camptotheca accuminata*) and paclitaxel (from the Pacific yew tree). About half of the anticancer drugs now under development also are derived from plant sources. In 1999, 23 of the 42 chemotherapeutic agents in Phase I study under National Cancer Institute auspices were of natural origin [9].

The standard method of developing anticancer agents from botanicals has been to "isolate and characterize the pure active constituents" [9] following mass screening of many thousands of botanicals. These active constituents are single chemical compounds that are chemically synthesized and administered to patients. Although patients may receive combinations of chemotherapeutic drugs, individual chemotherapeutic agents in widespread use contain a single active compound.

The rationale for this approach has never been made explicit. It is clear that research on a single compound is less complex than research on an agent that contains many compounds, particularly when the concentrations of these may vary from batch to batch. Moreover, study of an agent that contains unknown components or known components with unknown properties, is conceptually problematic. But investigative and conceptual expediency is distinct from efficacy and safety. The lack of scientific attention given to whole botanicals, compared to single compounds extracted from plants, is arguably not because the former are known to be ineffective or unsafe, it is because they are difficult to study.

Anticancer activity of whole botanicals: synergy and buffering

There are several reasons that whole botanical extracts, containing many compounds, may be of benefit in cancer treatment. First, different components in a botanical may have complementary or synergistic activities. The classic demonstration is that of Hosoya [10], who studied a mixture of four botanicals used to treat asthma. Only one botanical (*Ephedra hoya*) had any significant activity in a cat model of electrically stimulated cough. However, the activity of the mixture was greater than *Ephedra hoya* alone. In other words, components of the drug that showed no inherent antitussive effect potentiated the effect of the active principle.

Similar phenomena have been described for anticancer effects. Some components of Sho-saiko-to, a botanical medicine containing extracts from several different plants, show cytostatic effects on cancer cells [11], while a different set of components display moderate cytotoxic properties [12]. Moreover, there is evidence that the remedy as a whole improves immune function [13]. Any single compound isolated from Sho-saiko-to

may not retain the cytostatic, cytotoxic and immune stimulant properties of the whole. Similarly, Huanglian (*Copitidis chinensis)* has marked antiproliferative effects on tumor cells *in vitro*. The major constituent of huanglian is berberine. Although berberine reduces the growth of tumor cells, the effect is less strong than that of the whole huanglian extract, suggesting that different components of huanglian contribute to an anticancer effect [14]. As a further example, Noni is a fruit extract that is a popular lay treatment for cancer. It has been shown to contain at least two constituents with possible anticancer activity, each of which acts by different mechanisms: direct cytotoxicity [15] and immune modulation [16].

Some authors have speculated that synergy of botanical medicines results from the existence of "redundancy and back-up mechanisms found in the key regulatory and metabolic pathways of the cell" [17]. For example, a regulatory molecule targeted by an agent may be substituted by a back-up molecule that is possibly less effective, but nonetheless ensures survival of the tumor cell. The combination of a number of different compounds may have synergistic activity by targeting both primary and backup mechanisms simultaneously[17].

A second possible advantage of whole botanical extracts concerns the potential to decrease adverse effects. High toxicity is associated with all current chemotherapy agents derived from plants. Indeed, some agents derived from plants have been dropped from development as a result of toxicity (bruceantin and maytansine are examples). Practitioners who specialize in botanical medicine have long claimed that use of whole plant extracts reduces toxicity because of "buffering" between different constituents [18]. A classic demonstration of "buffering" is that 1% citral often causes sensitization when applied topically, whereas 4% lemongrass oil (which is 85% citral) is well tolerated [19].

There is some preliminary evidence that botanicals with possible effects against cancer can be used in doses that results in low toxicity. Toxicities seen in recent clinical trials of botanicals in cancer populations are far less severe than those typically reported in early phase trials of conventional cancer agents [5], [6]. Projections of effective doses based on preclinical data are well within the ranges used clinically by botanical medicine practitioners, apparently with extremely low toxicity. In the case of Sho-saiko-to, for example, the ED_{50} is in the region of 300 μg / ml for a hepatoma cell line [12]. This corresponds to a concentration of glycyrrhizin, a major component, of 1.5 μg / ml. The concentration of glycyrrhizin found in the blood after a normal daily dose is 1.2 μg / ml [20].

CURRENT EVIDENCE ON ANTICANCER BOTANICALS

Botanicals of promising scientific interest

Kampo medicines. Kampo medicines are traditional Japanese botanical formulas, each composed of 5 to 12 different botanicals. Two kampo medicines of particular interest in cancer are Sho-saiko-to and Juzen-taiho-to. Sho-saiko-to has demonstrated marked antiproliferative effects on various cancer lines, particularly hepatoma (see for example,

Yano et al [12]) and has been shown to inhibit development and metastasis of lung carcinoma [21] and melanoma [22]. It is known to have immune stimulant properties in humans [23,24]. In a Phase III randomized trial, two hundred and sixty patients with cirrhosis were randomized to treatment with Sho-saiko-to or control [25]. At five years, Sho-saiko-to led to a one-third reduction in the incidence of hepatocellular carcinoma (23% v. 34%) and a 40% reduction in deaths (24% v. 40%). Analyses of these data suggests that Sho-saiko-to has multifactorial action, both reducing the incidence of hepatic cancer and acting as a hepatoprotective.

Juzen-taiho-to is another Kampo botanical formula with anticancer activity. It has been demonstrated to prevent colorectal metastases to the liver in mouse models [26, 27] and has been shown to reduce the toxicity of platinum agents, apparently without compromising their antitumor effects [28, 29].

PC-SPES. PC-SPES is a recently developed botanical for the treatment of prostate cancer. It consists of eight different plant extracts, including some, such as saw palmetto, that have known estrogenic activity. A number of Phase II studies have been conducted on PC-SPES. PSA declines have been reported in 8 of 8 [30] and 57 of 69 patients [31]. Studies restricting inclusion to those with androgen independent disease have reported PSA declines in 20 of 23 [32] and 13 of 16 patients [33]. Significant improvements in pain and quality of life have also been reported [33]. The largest and most carefully implemented study to date is Small et al.'s two-stage, Phase II trial of PC-SPES in 70 patients with prostate cancer. Response was defined in terms of a reduction in prostate specific antigen (PSA) levels greater than 50% from baseline. All 32 patients with androgen-dependent cancer experienced PSA declines greater than 80%. PSA was at undetectable levels in 26. At median follow-up of 64 weeks, no patient had progressed objectively or in terms of PSA. Over half of the patients with androgen-independent disease had a PSA response, the median duration of which was 18 weeks. PC-SPES was associated with a number of endocrine side-effects. All patients reporting libido at baseline reported a decrease in libido on therapy. Similarly, all 15 patients who could achieve erection before therapy lost the ability to do so. PC-SPES also led to the development of gynecomastia or mastodynia in almost all patients and hot flashes in about one-third of patients [5]. Despite these encouraging results, it would be wise to be cautious about PC-SPES: it is unknown how predictive PSA is of survival in the context of botanical therapy and a survival advantage has yet to be shown.

β-glucan mushroom extracts. Many mushrooms used in Oriental botanical medicine contain β-glucans, a class of polysaccharide molecule. The anti-cancer effects of these agents have been widely studied. Almost all of this research has taken place in Japan, where several mushroom extracts are licensed and used for cancer.

Mushroom-derived β-glucans appear to have immune stimulant effects in both animal [34 - 37], and human models [38, 39]. There are a large number of animal studies showing anti-cancer activity. Typical studies have found that mushroom extracts reduce tumor weight of both breast carcinoma [40] and sarcoma [41], prevent metastasis of prostate cancer, [42], reduce hepatic and colon tumors in combination with cyclophosphamide

[43] and prevent induced bladder [44] and liver [45] tumors. A overview of these studies given by Borchers [46]. There have been several reports of synergism between vaccine therapies and β-glucans. In one model, suppression of in vivo growth of a colon cancer line by a monoclonal antibody was enhanced by concurrent treatment with a mushroom extract [47].

Most human trials of mushroom-derived β-glucans have studied PSK, an extract of *Coriolus versicolor,* or SPG, which extracted from the culture medium of *Schizophyllum commune* Fries. Trials typically compared chemotherapy or radiotherapy plus β-glucan or conventional treatment alone. Trials have found superior survival on PSK compared to controls in both gastrectomy [48, 49] and esophagectomy patients [50]. Results have been less encouraging in breast cancer [51, 52] and leukemia [53]. SPG was slightly but not significantly superior to control for gastrectomy, though in a sub-group analysis, improved survival was seen in patients with curative resection [54, 55]. The most encouraging results for SPG are for cervical cancer, with trials demonstrating improvements in survival [56] and increased rates of tumor response [57].

The two largest randomized trials of mushroom extracts in cancer have studied colorectal malignancy. In the first, 120 patients with advanced colorectal cancer undergoing curative resection were randomized to PSK or placebo starting 10 - 15 days after surgery. At the ten year follow-up, there were statistically significant differences between groups for both disease-free and overall survival. Median survival in the PSK group was approximately five years compared to just over four years in controls [58]. A subsequent trial randomized 462 colorectal cancer patients scheduled for curative resection to chemotherapy (mitomycin C and 5-FU) alone or chemotherapy plus PSK [59].Both disease-free and overall survival were significantly higher in the PSK group (three year rates 77.2% v. 67.7% and 85.8% v. 79.25.)

Huanglian. An extract of *Coptis chinensis*, known as huanglian, has been shown to inhibit topoisomerase I at levels comparable to camptothecins [60]. It has potent effects on growth and colony formation of gastric and colon lines, apparently by inhibiting cyclin B_1 [14]. A Phase I trial of huanglian is currently underway at Memorial Sloan-Kettering Cancer Center.

Green tea. Interest in green tea as an anticancer botanical originally stemmed from epidemiological studies demonstrating lower rates of various cancers, particularly colorectal cancer, in Chinese and Japanese green tea drinkers[61]. In a typical study, tea consumption was compared in cancer patients and matched controls in Shanghai: odds ratios for colon and rectal cancer amongst those with the highest consumption were 0.6 to 0.8 compared to those who did not consume tea regularly [62]. Green tea has been shown to prevent induced colorectal tumors in animals models[63, 64] and to have a direct, though moderate, inhibitory effect on cell growth [65, 66]. Though green tea is being actively pursued for a possible chemopreventive role[67], its activity as a cancer treatment has yet to be defined. A recent Phase I trial of a green tea extract reported a number of caffeine-related toxicities, such as agitation and insomnia. These were mild

and reversed on discontinuation of treatment. No objective responses to treatment were noted [6].

Popular botanicals

Essiac. Essiac was developed initially by a Native Canadian healer and popularized by a nurse, Rene Caisse. This product consists of four botanicals: burdock, Turkey rhubarb, sorrel, and slippery elm. A review reported in the Canadian Medical Association Journal reported no published research on Essiac [68], but it remains in popular use.

Mistletoe. Mistletoe extracts, which are more widely known by the trade names Iscador, Helixor and Eurixor, are popular cancer treatments in Europe and are available in some mainstream European cancer clinics. Unlike many herbal treatments, mistletoe extracts have been subject to randomized trials in cancer. A systematic review of these trials [69] reported serious methodological shortcomings in most studies. More recent trials have been larger and more methodologically rigorous and have reported no survival benefit in patients with malignant melanoma [70] or head and neck cancer [71]. A small trial in glioma had slightly more encouraging findings, with statistically significant differences between groups for one outcome in one subgroup [72]. Given the possibility of a false positive from multiple testing and the small number of patients, the findings require a confirmatory trial.

Noni. A botanical currently of particular popularity amongst cancer patients in noni (*Morinda citrifolia*). In many ways it is a typical unproved therapy: it is a natural product; it is said to have been used for "thousands of years" by "traditional Polynesian healers"; the discovery of its use in cancer is somewhat colorful, involving a miraculous cure of a pet dog; claims made for noni are ambiguous and implausible, such as it being a "strong blood purifier" and "cleans(ing) the body of harmful bacteria"'; the mechanisms of action is said to be "xeronine", a substance that has not been described elsewhere in the chemical or medical literature[73]. Interestingly, there is at least some scientific evidence in favor of noni. Noni has been shown to increase the lifespan of syngeneic mice implanted with Lewis lung carcinoma [74]. Moreover, a compound has been extracted from noni which shows potent tyrosine kinase inhibition [75]; an immunomodulatory polysaccharide has also been identified[76]. However, there do not appear to have been any human trials of this agent.

Pau d'arco tea. Pau d'arco tea is said to be an old Inca Indian remedy for many illnesses, including cancer. Made from the bark of an indigenous South American evergreen tree, its active ingredient, lapachol, has been isolated. Although lapachol showed antitumor activity in animal studies [77], it does not appear to affect human malignancies[78]. The tea can induce nausea and vomiting.

METHODOLOGICAL PROBLEMS IN STUDYING BOTANICALS

Quality control

Biological variation is a key issue in botanical medicines. It is known that small differences in genetics, soil, temperature, moisture and time of harvesting can lead to significant differences in the concentration of important constituents. For example, one of the active ingredient of oregano oil is thymol, which exhibits antimicrobial activity (it is a constituent of mouthwashes such as Listerine [79]) and is a calcium channel antagonist [80]. The concentration of thymol in the essential oil of oregano growing wild in the east Mediterranean varies from 85% to 4% [81]. This suggests that the clinical action of oregano oil may differ depending on where the plant was harvested. Time of harvesting has similarly been shown to affect the content of botanical medicines: the ratios of limonene to (E)-anethole (a calcium channel antagonist[80]) in oils from fennel plants harvested at different stages are approximately 4:5; 1:1; 16:1 [82].

To deal with such variation, manufacturers of botanical medicines typically choose one or two constituents as markers for quality control. Sho-saiko-to, for example, is standardized to contain a certain percentage of baicalin, glycyrrhizin and saikosaponin. St John's wort, which is used to treat depression [83], is standardized on its hypericin content. A similar approach is taken to pharmacokinetic analysis, where the concentration of one or two constituents in the blood is measured over time. In the recent trial of green tea for example, plasma concentrations of caffeine and epigallocatechin gallate (a constituent that inhibits cell lines *in vitro* [84]), were measured over a twenty-four hour period [6].

Using single constituents as markers for a botanical's quality and pharmacokinetics is a practical and simple solution. The problem with such an approach is that the exact relationship between the constituents of a botanical and its clinical effect have rarely been characterized fully. In the case of St John's wort, constituents other than hypericin are thought to contribute to its antidepressant properties [85]. Two preparations containing identical amounts of hypericin may in theory, differ in their clinical effects. Similarly, a dosing schedule of green tea based on epigallocatechin gallate may not be sufficient to provide an appropriate dose of other constituents known to have anti-cancer effects [86].

Phase I trials

An important purpose of a Phase I trial is to determine the most appropriate dose to take forward to clinical trials. In the case of cytotoxic chemotherapy agents, it is usually assumed that higher doses are the most effective and that toxicity is a surrogate for efficacy: an agent that inhibits production of blood cells and leads to hematologic toxicity, for example, is also likely to decrease proliferation of cancer cells. Accordingly, Phase I trials of cytotoxics attempt to determine a maximum-tolerated dose (MTD) by increasing the dose received by successive cohorts of patients until severe acute toxicities result. Chronic toxicities are rarely measured because most cytotoxics are taken over a limited period of time [87].

This Phase I methodology is so ubiquitous that it has been adopted almost without question, even for the study of botanicals [6]. But it is not clear that the ideal dose of a botanical medicine will be the highest that can be tolerated, particularly given that many appear to be without inherent cytotoxicity and act through an immune stimulant mechanism. Moreover, many botanicals are relatively benign, and it is plausible that these would not cause acute, severe toxicities even if taken at very high doses. Botanicals are taken daily over months and years [5], [25]and the effects of chronic administration therefore need to be assessed.

Phase I trials of biologics may provide an alternative model for dose-finding of anti-cancer botanicals. In a typical study of, say, a vaccine, a number of specific dose levels are pre specified. Whilst toxicity is assessed at each dose level, the primary outcome is to determine the dose level that maximizes a surrogate endpoint of efficacy, such as a serum antibody titre. The problem for many botanicals would be defining the surrogate endpoint. Unlike biologics, botanicals have not been specially developed to act via a specific mechanism and indeed the mechanism of action may not be fully characterized. Furthermore, there may be insufficient basic research to specify the particular doses to be tested.

Phase II trials

The endpoint of most Phase II trials of anticancer agents is "response": a rapid reduction in the size of a tumor. Traditional cytotoxic agents cannot be administered over long periods of time and so tumor regression must be rapid for the agent to be considered of value. As a tumor response is extremely unlikely to occur in an untreated patient, it can usually be ascribed to a treatment effect. Accordingly, Phase II trials can use a single arm design.

It seems unlikely that any botanical would lead to rapid regression of a tumor. A traditional, single arm Phase II with tumor response as an endpoint therefore seems inappropriate. Other endpoints, such as stable disease or overall survival, need to be defined. As disease stabilization following an anticancer treatment cannot necessarily be ascribed to the treatment, such endpoints may require alternative designs, such as the use of a concurrent or historical comparative arm.

CONCLUSION

At the turn of the 20th century, about half of the entries in the US pharmacopoeia were based on plants [88]. These medicines were not discarded because research demonstrated them to be harmful or ineffective, but, apparently, because they were too complex to study. As medical science and technology have advanced, and as the mutual distrust between conventional medicine and "alternative" practices has diminished, it may be time to re-evaluate the possibilities of botanical medicine. There are a number of theoretical reasons why such medicines may be of benefit in cancer. There are also some provocative preliminary data. What is required is a more systematic effort to study anticancer botanicals. Careful attention needs to given to the problem of drug standardization and to appropriate adaptations of Phase I and II trial methodology. For

cancer patients currently confronted by a bewildering array of botanical products, such research will provide information to guide healthcare choices. For future patients, it offers the hope of treatment combinations that are less toxic or more effective than contemporary therapies.

References

1 Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M,Kessler RC. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 280:1569-75, 1998

2 Boon H, Stewart M, Kennard MA, Gray R, Sawka C, Brown JB, McWilliam C, Gavin A, Baron RA, Aaron D, Haines Kamka T. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. J Clin Oncol 18(13):2515-21, 2000

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

4 Kao GD, Devine P. Use of complementary health practices by prostate carcinoma patients undergoing radiation therapy. Cancer 88(3):615-9, 2000

5 Small EJ, Frohlich MW, Bok R, Shinohara K, Grossfeld G, Rozenblat Z, Kelly WK, Corry M, Reese DM. Prospective Trial of the Herbal Supplement PC-SPES in Patients With Progressive Prostate Cancer. J Clin Oncol 18(21):3595-3603, 2000

6 Pisters KM, Newman RA, Coldman B, Shin DM, Khuri FR, Hong WK, Glisson BS, Lee JS. Phase I trial of oral green tea extract in adult patients with solid tumors. J Clin Oncol 19(6):1830-8, 2001

7 http://nccam.nih.gov/nccam/fi/concepts/nov2000/herbal.html accessed April 20. , 2001

8 Cragg GM, Newman DJ, Weiss RB. Coral reefs, forests, and thermal vents: the worldwide exploration of nature for novel antitumor agents. Semin Oncol 24(2):156-63, 1997

9 Cragg GM, Newman DJ. Discovery and development of antineoplastic agents from natural sources. Cancer Invest 17(2):153-63, 1999

10 Hosoya E. Scientific evaluation of Kampo prescriptions using modern technology. In: Hosoya E and Yamamura Y (Eds). Recent advances in pharmacology of Kampo (Japanese herbal) medicines. Amsterdam: Excerpta Medica 1988

11 Okita K, Li Q, Murakamio T, Takahashi M. Anti-growth effects with components of Sho-saiko-to (TJ-9) on cultured human hepatoma cells. Eur J Cancer Prev 2(2):169-75, 1993

12 Yano H, Mizoguchi A, Fukuda K, Haramaki M, Ogasawara S, Momosaki S, Kojiro M. The herbal medicine sho-saiko-to inhibits proliferation of cancer cell lines by inducing apoptosis and arrest at the G0/G1 phase. Cancer Res 54(2):448-54, 1994

13 Kok LD, Wong CK, Leung KN, Tsang SF, Fung KP, Choy YM. Activation of the anti-tumor effector cells by Radix bupleuri. Immunopharmacology 30(1):79-87, 1995

14 Li X, Tong W, Bornmann W, Schwartz GK. Huanglian, Chinese herbal extract, inhibits cell growth by suppressing the expression of cyclin B1 inhibiting CDC2 kinase activity in human cancer cells. Molecular Pharmacology (in press)

15 Hiwasa T, Arase Y, Chen Z, Kita K, Umezawa K, Ito H, Suzuki N. Stimulation of ultraviolet-induced apoptosis of human fibroblast UVr-1 cells by tyrosine kinase inhibitors. FEBS Lett 444(2-3):173-6, 1999

16 Hirazumi A, Furusawa E. An immunomodulatory polysaccharide-rich substance from the fruit juice of Morinda citrifolia (noni) with antitumour activity. Phytother Res 13(5):380-7, 1999

17 Darzynkiewicz Z, Traganos F, Wu JM, Chen S. Chinese herbal mixture PC SPES in treatment of prostate cancer (Review). Int J Oncol 17(4):729-36, 2000

18 Vickers A, Zollman C. ABC of complementary medicine: herbal medicine. BMJ 319(7216):1050-3, 1999

19 Opdyke DL. Inhibition of sensitization reactions induced by certain aldehydes. Food Cosmet Toxicol 14(3):197-8, 1976

20 Mizoguchi Y, Kawada N, Ichikawa Y, Tanabe I, Mizuno M, Tomekawa K, Hasegawa I, Morisawa S, Yamamoto S. The effects of sho-saiko-to on interluekin production I production by hepatic sinusoidal endothelial cells. J Med Pharm Soc 6:172-6, 1989
21 Ito H, Shimura K. Effects of a blended Chinese medicine, xiao-chai-hu-tang, on Lewis lung carcinoma growth and inhibition of lung metastasis, with special reference to macrophage activation. Jpn J Pharmacol 41(3):307-14, 1986
22 Kato M, Liu W, Yi H, Asai N, Hayakawa A, Kozaki K, Takahashi M, Nakashima I. The herbal medicine Sho-saiko-to inhibits growth and metastasis of malignant melanoma primarily developed in ret-transgenic mice. J Invest Dermatol 111(4):640-4, 1998
23 Kaneko M, Kawakita T, Tauchi Y, Saito Y, Suzuki A, Nomoto K. Augmentation of NK activity after oral administration of a traditional Chinese medicine, xiao-chai-hu-tang (shosaiko-to). Immunopharmacol Immunotoxicol 16(1):41-53, 1994
24 Yamashiki M, Kosaka Y, Nishimura A, Takase K, Ichida F. Efficacy of a herbal medicine "sho-saiko-to" on the improvement of impaired cytokine production of peripheral blood mononuclear cells in patients with chronic viral hepatitis. J Clin Lab Immunol 37(3):111-21, 1992
25 Oka H, Yamamoto S, Kuroki T, Harihara S, Marumo T, Kim SR, Monna T, Kobayashi K, Tango T. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). Cancer 76(5):743-9, 1995
26 Ohnishi Y. Fujii H. Hayakawa Y. Sakukawa R. Yamaura T. Sakamoto T.Tsukada K. Fujimaki M. Nunome S. Komatsu Y. Saiki I. Oral administration of a Kampo (Japanese herbal) medicine Juzen-taiho-to inhibits liver metastasis of colon 26-L5 carcinoma cells. Japanese Journal of Cancer Research 89(2):206-13, 1998
27 Onishi Y. Yamaura T. Tauchi K. Sakamoto T. Tsukada K. Nunome S.Komatsu Y. Saiki I. Expression of the anti-metastatic effect induced by Juzen-taiho-to is based on the content of Shimotsu-to constituents. Biological & Pharmaceutical Bulletin 21:761-5, 1998
28 Kiyohara H. Matsumoto T. Komatsu Y. Yamada H. Protective effect of oral administration of a pectic polysaccharide fraction from a Kampo (Japanese herbal) medicine "Juzen-Taiho-To" on adverse effects of cis-diaminedichloroplatinum. Planta Medica. 61:531-34, 1995
29 Sugiyama K. Ueda H. Ichio Y. Yokota M. Improvement of cisplatin toxicity and lethality by juzen-taiho-to in mice. Biological & Pharmaceutical Bulletin. 18:53-8, 1995
30 DiPaola RS, Zhang H, Lambert GH, Meeker R, Licitra E, Rafi MM, Zhu BT, Spaulding H, Goodin S, Toledano MB, Hait WN, Gallo MA. Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. New England Journal of Medicine 339(12):785-91, 1998
31 de la Taille A, Buttyan R, Hayek O, Bagiella E, Shabsigh A, Burchardt M, Burchardt T, Chopin DK, Katz AE. Herbal therapy PC-SPES: in vitro effects and evaluation of its efficacy in 69 patients with prostate cancer. J Urol 164(4):1229-34, 2000
32 Oh WK, George DJ, Hackmann K, Manola J, Kantoff PW. Activity of the herbal combination, PC-SPES, in the treatment of patients with androgen-independent prostate cancer. Urology 57(1):122-6, 2001
33 Pfeifer BL, Pirani JF, Hamann SR, Klippel KF. PC-SPES, a dietary supplement for the treatment of hormone-refractory prostate cancer. BJU Int 85(4):481-5, 2000
34 Adachi K, Nanba H, Kuroda H. Potentiation of host-mediated antitumor activity in mice by beta-glucan obtained from Grifola frondosa (maitake). Chem Pharm Bull (Tokyo) 35(1):262-70, 1987
35 Suzuki I, Hashimoto K, Oikawa S, Sato K, Osawa M, Yadomae T. Antitumor and immunomodulating activities of a beta-glucan obtained from liquid-cultured Grifola frondosa. Chem Pharm Bull (Tokyo) 37(2):410-3, 1989
36 Suzuki I, Hashimoto K, Ohno N, Tanaka H, Yadomae T. Immunomodulation by orally administered beta-glucan in mice. Int J Immunopharmacol 11(7):761-9, 1989
37 Abel G, Czop JK. Stimulation of human monocyte beta-glucan receptors by glucan particles induces production of TNF-alpha and IL-1 beta. Int J Immunopharmacol 14(8):1363-73, 1992
38 Kato M, Hirose K, Hakozaki M, et al. Induction of gene expression for immunomodulating cytokines in peripheral blood mononuclear cells in response to orally administered PSK , an immunomodulating protein-bound polysaccharide. Caner Immunology Immunotherapy 40:152-6, 1995
39 Kano Y, Kakuta H, Hashimoto J. Effect of sizofiran on regional lymph nodes in patients with head and neck cancer. Biotherapy 9(4):257-62, 1996

40 Yamada Y, Nanba H, Kuroda H. Antitumor Effect of Orally Administered Extracts from Fruit Body of Grifola Frondosa (Maitake). Chemotherapy 38(8):790-96, 1990
41 Hishida I, Nanba H, Kuroda H. Antitumor activity exhibited by orally administered extract from fruit body of Grifola frondosa (maitake). Chem Pharm Bull (Tokyo) 36(5):1819-27, 1988
42 Kobayashi H, Matsunaga K, Oguchi Y. Antimetastatic effects of PSK (Krestin), a protein-bound polysaccharide obtained from basidiomycetes: an overview. Cancer Epidemiol Biomarkers Prev 4(3):275-81, 1995
43 Abe S, Tsubouchi J, Takahashi K, Yamazaki M, Mizuno D. Combination therapy of murine tumors with lentinan plus lipopolysaccharide plus cyclophosphamide. Gann 73(6):961-7, 1982
44 Kurashige S, Akuzawa Y, Endo F,, Kurashige S, Akuzawa Y, Endo F. Effects of Lentinus edodes, Grifola frondosa and Pleurotus ostreatus administration on cancer outbreak, and activities of macrophages and lymphocytes in mice treated with a carcinogen, N-butyl-N-butanolnitrosoamine. Immunopharmacol Immunotoxicol 19(2):175-83, 1997
45 Nanba H. Activity of maitake D-fraction to inhibit carcinogenesis and metastasis. Ann N Y Acad Sci 768:243-5, 1995
46 Borchers AT, Stern JS, Hackman RM, Keen CL, Gershwin ME. Mushrooms, tumors, and immunity. Proc Soc Exp Biol Med 221(4):281-93, 1999
47 Kanoh T, Saito K, Matsunaga K, Oguchi Y, Taniguchi N, Endoh H, Yoshimura M, Fujii T, Yoshikumi C. Enhancement of the antitumor effect by the concurrent use of a monoclonal antibody and the protein-bound polysaccharide PSK in mice bearing a human cancer cell line. In Vivo 8(2):241-5, 1994
48 Niimoto M, Hattori T, Tamada R, Sugimachi K, Inokuchi K, Ogawa N. Postoperative Adjuvant Immunochemotherapy with Mitomycin C, Futraful, and PSK for Gastric Cancer. An Analysis of Data on 579 Patients followed for Five Years. Japanese Journal of Surgery 18(6):681-686, 1988
49 Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. The Lancet 343:1122-26, 1994
50 Ogoshi K, Satou H, Isono K, Mitomi T, Endoh M, Sugita M. Immunotherapy for esophageal cancer. A randomized trial in combination with radiotherapy and radiochemotherapy. Cooperative Study Group for Esophageal Cancer in Japan. Am J Clin Oncol 18(3):216-22, 1995
51 Toi M, Hattori T, Akagi M, Inokuchi K, Orita K, Sugimachi K, Dohi K, Nomura Y, Monden Y, Hamada Y, et al. Randomized adjuvant trial to evaluate the addition of tamoxifen and PSK to chemotherapy in patients with primary breast cancer. 5-Year results from the Nishi-Nippon Group of the Adjuvant Chemoendocrine Therapy for Breast Cancer Organization. Cancer 70(10):2475-83, 1992
52 Iino Y, Yokoe T, Maemura M, Horiguchi J, Takei H, Ohwada S, Morishita Y. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. Anticancer Res 15(6B):2907-11, 1995
53 Ohno R, Yamada K, Masaoka T, et al. A randomized trial of chemoimmunotherapy of acute nonlymphocytic leukemia in adults using a protein-bound polysaccharide preparation. Cancer Immunology Immunotherapy 18:149-54, 1984
54 Fujimoto S, Furue H, Kimura T, Kondo T, Orita K, Taguchi T, Yoshida K, Ogawa N. Clinical evaluation of schizophyllan adjuvant immunochemotherapy for patients with resectable gastric cancer--a randomized controlled trial. Jpn J Surg 14(4):286-92, 1984
55 Fujimoto S, Furue H, Kimura T, Kondo T, Orita K, Taguchi T, Yoshida K, Ogawa N. Clinical outcome of postoperative adjuvant immunochemotherapy with sizofiran for patients with resectable gastric cancer: a randomised controlled study. Eur J Cancer 27(9):1114-8, 1991
56 Okamura K, Suzuki M, Chihara T, Fujiwara A, Fukuda T, Goto S, Ichinohe K, Jimi S, Kasamatsu T, Kawai N, et al. Clinical evaluation of sizofiran combined with irradiation in patients with cervical cancer. A randomized controlled study; a five-year survival rate. Biotherapy 1(2):103-7, 1989
57 Noda K, Takeuchi S, Yajima A, Akiya K, Kasamatsu T, Tomoda Y, Ozawa M, Sekiba K, Sugimori H, Hashimoto S, et al. Clinical effect of sizofiran combined with irradiation in cervical cancer patients: a randomized controlled study. Cooperative Study Group on SPG for Gynecological Cancer. Jpn J Clin Oncol 22(1):17-25, 1992
58 Torisu M, Hayashi Y, Ishimitsu T, et al. Significant prolongation of disease -free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. Cancer Immunology Immunotherapy 31:261-8, 1990

59 Mitomi T, Tsuchiya S, Iijima N, Aso K, Suzuki K, Nishiyama K, Amano T, Takahashi T, Murayama N, Oka H, et al. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. The Cooperative Study Group of Surgical Adjuvant Immunochemotherapy for Cancer of Colon and Rectum (Kanagawa). Dis Colon Rectum 35(2):123-30, 1992
60 Kobayashi Y, Yamashita Y, Fujii N, Takaboshi K, Kawakami T, Kawamura M, Mizukami T, Nakano H. Inhibitors of DNA topoisomerase I and II isolated from the Coptis rhizomes. Planta Med 61(5):414-8, 1995
61 Kohlmeier L, Weterings KG, Steck S, Kok FJ. Tea and cancer prevention: an evaluation of the epidemiologic literature. Nutr Cancer 27(1):1-13, 1997
62 Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. Int J Cancer 70(3):255-8, 1997
63 Hirose M, Hoshiya T, Akagi K, Takahashi S, Hara Y, Ito N. Effects of green tea catechins in a rat multi-organ carcinogenesis model. Carcinogenesis 14(8):1549-53, 1993
64 Hirose M, Takahashi S, Ogawa K, Futakuchi M, Shirai T, Shibutani M, Uneyama C, Toyoda K, Iwata H. Chemoprevention of heterocyclic amine-induced carcinogenesis by phenolic compounds in rats. Cancer Lett 143(2):173-8, 1999
65 Yang GY, Liao J, Kim K, Yurkow EJ, Yang CS. Inhibition of growth and induction of apoptosis in human cancer cell lines by tea polyphenols. Carcinogenesis 19(4):611-6, 1998
66 Chen ZP, Schell JB, Ho CT, Chen KY. Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett 129(2):173-9, 1998
67 Kelloff GJ, Crowell JA, Steele VE, Lubet RA, Malone WA, Boone CW, Kopelovich L, Hawk ET, Lieberman R, Lawrence JA, Ali I, Viner JL, Sigman CC. Progress in cancer chemoprevention: development of diet-derived chemopreventive agents. J Nutr 130(2S Suppl):467S-471S, 2000
68 Kaegi E. Unconventional therapies for cancer: 1. Essiac. The Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. Can Med Assoc J 158(7):897-902, 1998
69 Kleijnen J. Knipschild P. Mistletoe treatment for cancer. Review of controlled trials in humans. Phytomedicine 1:255-60, 1994
70 McNamee D. Mistletoe extract ineffective in melanoma (news). Lancet 354:1101, 1999
71 Steuer Vogt MK, Bonkowsky V, Ambrosch P, Scholz M, Neiss A, Strutz J, Hennig M, Lenarz T, Arnold W. The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. Eur J Cancer 37(1):23-31, 2001
72 Lenartz D, Dott U, Menzel J, Schierholz JM, Beuth J. Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 20(3B):2073-6, 2000
73 http://www.go-symmetry.com/Noni.htm accessed 08/04/00
74 Hirazumi A, Furusawa E, Chou SC, Hokama Y. Anticancer activity of Morinda citrifolia (noni) on intraperitoneally implanted Lewis lung carcinoma in syngeneic mice. Proc West Pharmacol Soc 37:145-6, 1994
75 Hiwasa T, Arase Y, Chen Z, Kita K, Umezawa K, Ito H, Suzuki N. Stimulation of ultraviolet-induced apoptosis of human fibroblast UVr-1 cells by tyrosine kinase inhibitors. FEBS Lett 444(2-3):173-6, 1999
76 Hirazumi A, Furusawa E. An immunomodulatory polysaccharide-rich substance from the fruit juice of Morinda citrifolia (noni) with antitumour activity. Phytother Res 13(5):380-7, 1999
77 da Consolacao M, Linardi F, de Oliveira MM, Sampaio MR. A lapachol derivative active against mouse lymphocytic leukemia P-388. J Med Chem 18(11):1159-61, 1975
78 Block JB, Serpick AA, Miller W, Wiernik PH. Early clinical studies with lapachol (NSC-11905). Cancer Chemother Rep 2 4(4):27-8, 1974
79 Fornell J, Sundin Y, Lindhe J. Effect of Listerine on dental plaque and gingivitis. Scand J Dent Res 83:18-23, 1975
80 Melzig M, Teuscher E. Investigations of the influence of essential oils and their main components on the adenosine uptake by cultivated endothelial cells. Planta Med 57(1):41-2, 1991
81 Ravid U, Putievsky E. Carvacrol and thymol chemotypes of east Meditarranean wild Labiatae herbs. In: Brunke EJ (Ed.). Progress in Essential Oil Research. Berlin, Walter de Gryter. 1986

82 Marotti M. Effects of variety and ontogenic stage on the essential oil composition and biological activity of fennel (Foeniculum vulgare Mill). J Essential Oil Res 6(1):57-62, 1994
83 Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's Wort for depression--an overview and meta-analysis of randomised clinical trials. BMJ 313(7052):253-8, 1996
84 Chen ZP, Schell JB, Ho CT, Chen KY. Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett 129(2):173-9, 1998
85 Linde K, Mulrow CD. St John's wort for depression (Cochrane Review). In: The Cochrane Library. Oxford: Update Software. 2000
86 Hirose M, Hoshiya T, Akagi K, Takahashi S, Hara Y, Ito N. Effects of green tea catechins in a rat multi-organ carcinogenesis model. Carcinogenesis 14(8):1549-53, 1993
87 Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. J Clin Oncol 18(3):684-92, 2000
88 Swerdlow JL.. Rediscovering the roots of modern medicine. Global Health and Environment Monitor 9(1):1, 2001