THE CANCER LETTER

Vol. 19 No. 15
April 9, 1993

Price $225 Per Year US, Canada.
$250 Per Year Elsewhere

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

Gene Therapy Appears To Benefit Two Children With ADA Deficiency, Scientist Tells Writers

The first two patients ever to undergo an attempt at treating their disease by altering their genes--two young girls with adenosine deaminase deficiency treated at NIH--are improving as a result of gene therapy, according to a former NCI scientist involved in the study.

Seven hundred days from the beginning of the study in which the patients' own blood cells are genetically corrected and returned to them by injection, the two girls, now ages 11 and 6, are showing signs that their immune systems are becoming healthier, said Kenneth Culver, a

(Continued to page 2)

In Brief

Hutchinson Begins Prostate Cancer Study; Meyer Named GWU Medical Dean; Nurses Win VA Posts

PROSTATE CANCER is the focus of a five-year study begun last month by the Fred Hutchinson Cancer Research Center with a $1.8 million grant from NCI. Principal investigator **Janet Stanford** will study 700 men under age 65 newly diagnosed with prostate cancer, and an equal number of men without prostate cancer to determine factors that may be contributing to the increase in prostate cancer incidence over the past decade. . . . **ROGER EMIL MEYER** was named vice president for medical affairs and executive dean of the George Washington Univ. Medical Center recently. Meyer is executive dean of the Univ. of Connecticut Medical School. He will take the position at GWU on Sept. 1. . . . **PRESIDENT CLINTON** has appointed two registered nurses, **Mary Lou Keener** and **Yvonne Santa Anna** to posts at the Dept. of Veterans Affairs. The nominations were supported by the American Nurses Assn. Keener was nominated to the post of general counsel. Santa Anna was nominated for assistant secretary for intergovernmental and public affairs. . . . **KENNETH McCARTY JR.** has joined the Pittsburgh Cancer Institute in endocrine oncology and pathology. McCarty, a breast disease specialist, was associate professor of pathology and assistant professor of medicine at Duke Univ. Medical Center. . . . **FOX CHASE** Cancer Center recently promoted three physicians and researchers. Promoted to senior member were **Peter O'Dwyer** and **Joseph Testa. Thomas Hamilton** was promoted to member. . . . **CLINICAL TRIALS GROUP** of the National Cancer Institute of Canada will hold a medical symposium, "The Purine Analogues: New Chemotherapy for Lymphoma and Leukemia," on April 16 in Montreal. Contact the Queen Elizabeth Hotel, phone 514/861-3511.

Gene Therapy Seems To Benefit First Two Patients With ADA Deficit

(Continued from page 1)

former NCI scientist, now director of clinical research for Genetic Therapy Inc., based in Gaithersburg, MD.

ADA is necessary for proper immune system functioning. ADA deficiency is an extremely rare disease. Children with the disease are kept in sterile environments, but still die from infections. A drug is available to boost the ADA level, PEG-ADA, costing about $250,000 for a year's treatment. The two girls were taking PEG-ADA, but their immune systems still were not properly functioning, Culver said.

After injections of the genetically altered cells, however, the ADA level of the first patient is 25 percent of normal, Culver said. The patient's parents have 50 percent of normal ADA; a person can have a functioning immune system with between 10 percent to 500 percent of "normal" ADA, Culver said at the annual American Cancer Society Science Writers Seminar, held last week in San Diego, CA.

At first, the investigators--Michael Blaese of NCI, French Anderson, formerly of the National Heart, Lung & Blood Institute, and Culver--gave the patients injections every six to eight weeks. Now they are giving the gene therapy about every six to eight weeks.

The first patient now is able to make antibodies against other blood types besides her own, and has normal immune responses to influenza vaccine.

Both patients now have tonsils, which they did not have prior to the gene therapy, Culver said. One of the girls has lymph nodes that were not present before.

In addition, the patients test positive when challenged with skin tests for tetanus and diphtheria.

"This is a very exiting result, suggesting that not only can T-cells circulate in blood, but also can relocate to other parts of the body," Culver said.

The first patient is now attending school regularly, and her sister, who did not have the disease but was kept home for fear she would introduce infections, also is going to school, Culver said.

The investigators are planning to try bone marrow transplant on the two patients with the hope of permanently altering the genetic makeup of their stem cells.

The first publication describing the results has been submitted to the "New England Journal of Medicine," Culver said.

Genetic Therapy Inc. is paying Culver's salary for a year to continue working on the NIH protocol with Blaese, but Culver began his own gene therapy protocol for brain tumors last December.

The protocol uses the herpes simplex-thymidine Kinase gene to confer "sensitivity" to the anti-herpes drug ganciclovir to brain tumors. The tumors then will be treated with ganciclovir by injection directly into the tumor using stereotactic guided surgery. This method produced complete tumor regression in 11 of 14 rats treated, Culver said.

"We don't get all the cells in all the animals," Culver said.

In the human trial, seven patients with metastatic brain tumors or glioblastoma multiforme have been treated. No patient has demonstrated evidence of toxicity. It is too early to determine the antitumor effect, Culver said.

Culver's collaborators on the study are Zivi Ram and Edward Oldfield.

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A high intake of saturated fat puts nonsmoking women at greater risk of lung cancer, according to a study conducted by NCI's Epidemiology and Biostatistics Program.

The case-control study, conducted in Missouri as part of an NCI study of radon exposure in households in that state, collected data on 600 lung cancer cases and 1,400 controls.

The effect of saturated fat was most pronounced for cases of adenocarcinoma, resulting in a five-fold increased risk for that type of lung cancer, according to Michael Alavanja, special assistant to Joseph Fraumeni, director of the NCI program.

Cholesterol and total fat consumption, found to be small to moderate risk factors in other published studies, did not have an independent effect in the NCI study, Alavanja said to the annual American Cancer Society Science Writers Seminar, held last week in San Diego, CA.

The effect of saturated fat was independent of

THE CANCER LETTER

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Subscription rate $225 per year North America, $250 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

exposure to environmental tobacco smoke, obesity, or whether a woman lived in an urban or rural area, Alavanja said.

Cases were nonsmoking white women between the ages of 30-84 with primary lung cancer who were reported to the Missouri Cancer Registry between June 1, 1986 and June 1, 1991. Tissue slides were reviewed for histologic verification for all cases where pathological material was available (77 percent).

Controls were a population-based sample selected randomly from Missouri driver's license files and lists of women signed up for Medicare.

The diet of the women four years prior to the study was determined by a self-administered questionnaire containing 60 food types. The food list and the nutrient values associated with it were developed using data from the Second National Health and Nutrition Examination Study (NHANES II).

Up to 20 percent of women diagnosed with lung cancer are nonsmokers, as many as 4,000 cases in the U.S.

Missouri was selected for the overall residential radon study because the state has a cancer registry and the population is very stable, allowing investigators to determine 30-year exposure histories, Alavanja said.

"While our findings support the public health admonition to reduce fat and saturated fat intake in our diet, additional etiologic studies are needed before we can fully understand the nature of this association," Alavanja said.

Strengths of the investigation were the evaluation of incident cases of lung cancer in a population-based setting, the relatively large number of nonsmoking women available for the study, and pathology review of most cases, Alavanja said.

Potential weaknesses were the large number of proxy respondents for the diet information and the limited food items list. The NCI researchers conducted the same analysis using only the subjects who provided self-reports of dietary intakes, and reached the same conclusions. A followup study will use a food questionnaire that includes 120 items.

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Two investigators from NCI's Laboratory of Pathology presented their research at the ACS Science Writers Seminar:

▶ Preliminary data are "encouraging" for carboxyamido-triazole, or CAI, a synthetic molecule in phase 1 trials for treatment of a variety of solid tumors, according to Elise Kohn, senior clinical investigator in NCI's Laboratory of Pathology. CAI appears to inhibit both metastasis and growth of tumor cells by blocking cell signaling.

"I'm very excited because this is a new mechanism of action for an anticancer drug," Kohn said. "I'd put it high on the excitability scale."

All of the steps in the "cascade" leading to metastasis require a signal transduction pathway leading to the mobilization of calcium within and to the cell, Kohn said. Blocking this signal might stop metastasis. This would offer an approach different than cytotoxic chemotherapy drugs which act by blocking cell division.

The laboratory devised an in vitro assay to screen drugs for their ability to block metastasis. Tumor cells that normally are able to migrate across a porous membrane in response to stimulants were unable to migrate after treatment with CAI. CAI also was selective, blocking only those cells known to use calcium in their signaling.

In another series of in vitro tests, Kohn determined that CAI also inhibited tumor cell growth. In animal testing, the drug reduced tumor size in mice bearing human ovarian cancer.

NCI filed an Investigational New Drug application for CAI, and in March 1992 opened a phase 1 study to patients with refractory solid tumors or lymphoma. Thirteen patients have been treated with oral CAI to date, and toxicity so far is mild nausea with rare vomiting, Kohn said. One patient had neutropenia, but with no complications.

CAI has resulted in tumor stabilization in all but one of the evaluable patients, Kohn said.

"The combination of its novel mechanism of action, suggestion of broad activity, and ease of administration makes CAI the first drug for a new therapeutic paradigm in which cancer is treated as a chronic disease, with long term therapy to stabilize tumor growth and block metastases," Kohn said.

Information on the phase 1 trial may be obtained by calling NCI at 1-800-4-CANCER and requesting the "CAI Report."

▶ Seven years ago, Patricia Steeg, research biologist in NCI's Laboratory of Pathology, identified a gene she called nm23 (nonmetastatic cDNA 23) which had RNA levels 10 times higher in two low metastatic melanoma cell lines than in five highly metastatic melanoma cell lines. This indicated that the gene was "turned off" in highly metastatic tumor cells.

Other laboratories have found that nm23 expression is lower in patients with more indolent tumors. Five published reports have found that high nm23 expression in primary breast cancer was associated with good prognosis.

The next question was whether putting nm23 back into a metastatic tumor cell would render the cell less

metastatic. Steeg found that one member of the nm23 gene family, nm23-H1, partially suppressed the metastatic ability of the MDA-MB-435 human breast cancer cell line.

NCI is negotiating with pharmaceutical companies to test a large panel of agents for their capacity to stimulate tumor cells to re-express their own nm23 gene, Steeg said.

"Assuming such screening assays are successful, we will determine the safety and efficacy in mice of any pharmaceutical agents identified, and then approach clinical trails," Steeg said. "It is my hope that, using new molecular approaches to drug screening such as nm23, we can identify new classes of pharmaceutical agents with potent anticancer activities."

Additional coverage of the ACS Science Writers Seminar will be contained in the April issue of ***The Clinical Cancer Letter.***

NIH Selects 16 Clinical Centers For Women's Health Initiative

Sixteen university medical programs around the country have been awarded contracts as "vanguard clinical centers" for the NIH Women's Health Initiative, the 15-year, $625 million study of heart disease, cancer, and osteoporosis.

The 16 centers were selected from 61 proposals. The average contract award per center amounts to nearly $10.5 million over the 15-year period.

The initiative, announced in the spring of 1991 (**The Cancer Letter**, May 31, 1991) is comprised of clinical trials and an observational study examining:

▶the effects of a low fat diet in preventing breast and colorectal cancer and heart disease;

▶the benefits and risks of hormone replacement therapy in preventing cardiovascular disease and osteoporotic fractures;

▶the effects of calcium and vitamin D supplements in preventing osteoporotic fractures and colorectal cancer.

"The work of this project is overdue," HHS Secretary Donna Shalala said. "This initiative is a first step toward equity for women's health research, and it needs to be followed up by ensuring the place of women's health in the mainstream of biomedical research."

"The Women's Health Initiative is NIH's commitment to redress the crucial medical knowledge gaps women continue to face today," said NIH Director Bernadine Healy. "Launching this national program will permanently put women's health concerns on the nation's research agenda."

The 16 centers are: Bowman Gray School of Medicine, Brigham & Women's Hospital Dept. of Medicine, Emory Univ. School of Medicine, Fred Hutchinson Cancer Research Center, Memorial Hospital of Rhode Island, Northwestern Univ. Medical School, State Univ. of New York at Buffalo, Univ. of Alabama at Birmingham, Univ. of Arizona, Univ. of California (Davis) School of Medicine, Univ. of California (San Diego) School of Medicine, Univ. of Iowa College of Medicine, Univ. of Medicine and Dentistry of New Jersey-New Jersey Medical School, Univ. of Minnesota Medical School, Univ. of Tennessee (Memphis).

The Fred Hutchinson Cancer Research Center in Seattle, WA, was awarded a $140 million contract last October to serve as the coordinating center for the initiative (**The Cancer Letter,** Oct. 23, 1992).

The centers will test, refine and implement the final study design and procedures to enroll women nationwide in the first stage of clinical trials by this September. By mid-1994, another 29 clinical centers will be added.

Altogether, 45 centers will carry out the WHI. It will involve more than 160,000 women ages 50-79.

The Studies

The WHI will be made up of:

▶A randomized controlled clinical trial will enroll about 60,000 postmenopausal women aged 50-79 years. Four years will be required for the full protocol development and recruitment, and nine years for followup. The trial will have three components, with overlapping enrollment of participants:

--50,000 women randomized to a low fat diet (20 percent of calories from fat; less than 7 percent of calories from saturated fat) or usual diet to assess effect on prevention of coronary heart disease, breast and colorectal cancer.

--25,000 women randomized to estrogen only, estrogen plus progestin, or placebo, to examine the effect on prevention of coronary heart disease, osteoporotic fractures, and/or increased risk of breast cancer.

--45,000 women randomized equally to calcium/vitamin D or placebo to assess the effect on prevention of osteoporotic fractures and colorectal cancer.

▶An observational study will examine the relationship between risk factors and biological markers to specific disease outcomes. About 100,000 postmenopausal women will be enrolled in the study and will be followed for nine years. Data will be collected on diets, environmental exposures, hormone

replacement therapy and oral contraceptive use.

▶A randomized trial in communities to test approaches to adoption of healthy behaviors such as appropriate diet, smoking cessation, exercise and early disease detection. Twenty matched pairs of communities will be randomized to intervention or control.

Each of the 45 centers will recruit 3,490 women over three years for the clinical trial and observational study.

A target of 20 percent minority enrollment has been set to ensure that data is relevant to minority populations. Four of the 16 vanguard centers will recruit at least 60 percent or more of their participants from minority populations. Those centers are Emory Univ. School of Medicine, Univ. of Alabama at Birmingham, Univ. of Arizona, and Univ. of California (San Diego). They were selected from 20 proposals in a minority pool.

"We will be vigilant in our efforts to ensure that the results of the Women's Health Initiative have meaning to all women from all socio-economic and racial backgrounds," said William Harlan, co-director of the WHI and associate director of the NIH Office of Disease Prevention.

Principal investigators from the vanguard centers held their first meeting last week in Seattle. A second meeting will be held April 20-21 in Bethesda, MD.

DCE Proposes AIDS-Cancer Registry For Funding Through $2 Mil. Contract

NCI's Div. of Cancer Etiology plans to establish a multi-state registry to match AIDS and cancer cases in the hope that better data will emerge about the types of cancer, trends, and demographics of persons with AIDS who get cancer.

DCE's Board of Scientific Counselors gave concept approval to funding the registry through a $2 million, five-year contract at a meeting last week.

DCE's Epidemiology & Biostatistics Program conducted a pilot test of the linkage system in Florida, California, metro Atlanta and New Jersey. The local cancer registries observed 83,434 PWAs diagnosed from 1981-92. The cancer incidence was compared to rates from NCI's Surveillance, Epidemiology & End Results registry from 1975-79, adjusted for the age, race and sex distribution of PWAs.

The pilot study suggested AIDS-associated cancer has a wider spectrum than scientists thought. Of the 32 cancer sites analyzed, for 24 there were no significant differences between incident cancers observed and expected. In the first six months after AIDS diagnosis, incidence rates were significantly increased for KS, NHL, Hodgkin's disease, lung cancer, leukemia, anal cancer, non-lymphomatous brain cancer and multiple myeloma. Review of tissues and medical records is required to confirm these findings, DCE staff said.

Following is the text of the concept statement:

Establishment and Analysis of a multi-state AIDS/Cancer Match Registry. Proposed new RFP, first year award $389,373, total $2,151,532 over five years. Project officers: Timothy Cote, William Blattner, Mitchell Gail, Epidemiology & Biostatistics Program.

Objectives of this procurement are to establish a multi-state AIDS/Cancer Match Registry:

1. To determine which malignancies occur with increased frequency among PWAs.

2. To monitor trends and generate projections of cancer cases among PWAs.

3. To compare demographic factors among PWAs with and without cancer and to detail tumor characteristics.

4. To identify PWAs with cancer from whom biological specimens may be obtained through tumor registries.

In the U.S., there is no central repository of identifying information for PWAs or cancer patients. Therefore, all linkage activities will be conducted at those state and local health departments where names and dates of birth are maintained. Although personal identifiers will be required for the linkage, personal identifiers will not be supplied to NCI, but will continue to reside within the state.

Linkage will begin only after approval from both an NCI and a local institutional review board. Linkage will be conducted exclusively on a stand-alone personal computer in accordance with local data management policies and will be conducted using a double-blinded protocol which does not disclose AIDS diagnoses to cancer registry officials nor disclose cancer diagnoses to AIDS registry officials. Much like the SEER and CDC-AIDs Surveillance registries, the MSACMR will lack identifying information; it will not contain name, day or month of birth, soundex, local registry number, or any other information which could be traced to individuals. However, the ability to trace biologic specimens will be retained through a locally maintained linking file.

We propose to conduct linkages in 1994 and 1999 of AIDS and cancer registries in New York City, Puerto Rico, New York State, New Jersey, San Francisco Bay Area, Sacramento, Los Angeles, San Diego, Metro Atlanta, Florida, Illinois, Connecticut, Massachusetts, Colorado, and Detroit. Together, these areas account for 75% of nationally reported AIDS cases. They also provide divergent populations in terms of race, sex and exposure category. For each area, review of the incidence rates for most cancers revealed good general agreement with overall SEER rates. Migration of PWAs, as measured by the discordance of residence reported on AIDS reports compared to death certificates, was less than 10% in each of these areas.

We propose two methods to compare the cancers among PWAs to cancers in the general population: one for cancers diagnosed after the date of AIDS diagnosis and one for cancers diagnosed on or before AIDS. In the first, we consider

PWAs as a cohort in which subjects entered the study on date of AIDS diagnosis. This cohort is followed forward until death (data now available through recently completed AIDS Surveillance/National Death Index matching system), cancer diagnosis (determined through linkage), or the common close date. Person-years of observation can be tabulated and standardized incidence ratios computed using conventional techniques.

The second analysis compares cancer prevalence (defined as the proportion of living people who had a cancer diagnosed in the previous five years) with the prevalence expected in a general population with ages, race, and sex matched to those of PWAs at AIDS diagnosis. Methods already have been developed for calculating expected prevalence from SEER incidence and survival data; observed prevalent cases are estimated by linkage to the AIDS registry.

The strength of this approach is its superior statistical power coupled with detailed cancer histology data. Using age-, sex-, and race-adjusted SEER rates we computed the minimum relative risk required to detect increased cancers among PWAs *currently available from the Multicenter AIDS Cohort Study, the AIDS Clinical Trials Group and the proposed* Multi-State AIDS/Cancer Match Registry. For each cohort we assumed one person-year of observation after AIDS diagnosis. These power calculations do not consider the accrual of new cases over the next five years; the MSACMR would grow in direct proportion to the AIDS epidemic which we expect would be faster than accrual into the MACS or ACTG (particularly with the new, broadened AIDS case definition). The power calculations consider incident cases only; cancer prevalences can be computed and compared to expected prevalence by the MSACMR but not by the MACS nor the ACTG.

When compared to the MACS and the ACTG, registry linkage has several limitations as a method of study:

1. Dates of seroconversion are unavailable and data on HIV-positive people who have not yet developed AIDS are limited. Although computation of cancer point prevalence at AIDS diagnosis permits consideration of cancers prior to AIDS, this does not substitute for prospective follow-up of HIV-infected/non-AIDS individuals. We expect, however, that the greatest cancer risk would occur when immunodeficiency is most severe, that is, at or after AIDS diagnosis. Twenty-three states have recently mandated reporting HIV positive individuals regardless of stage of infection. Where possible we intend to link these lists to cancer registries.

2. *In contrast to the MACS and ACTG, the clinical data collected through AIDS surveillance are restricted to events at the time of AIDS diagnosis. Surveillance data on possible confounders (e.g., smoking, occupation) are also limited.*

3. Ascertainment bias may increase the likelihood of cancer diagnosis among PWAs because they may receive medical care more than the general population. We plan to use existing data sources to quantify the magnitude of potential ascertainment bias.

4. Reporting is done by jurisdiction of residence. PWAs who develop AIDS as a resident of one jurisdiction may migrate and develop cancer as a resident of their new jurisdiction. This could lead to underestimation of cancer risk among PWAs. Data have just become available which permit comparison of residence at AIDS reporting to residence at death. Monitoring trends in migration of PWAs will aid interpretation of results.

AACI Statement On Cancer Centers Presented To Reform Task Force

The Assn. of American Cancer Institutes has presented a statement of its position on health care reform to staff of the Presidential Task Force on Health Care Reform.

Following is the text of the statement:

"Since the passage of the National Cancer Act in 1971, the cancer centers across the United States have played a leadership role in defining high quality cancer care and must be allowed to continue this effort as we move toward a delivery system of 'managed care.'

▶ The Assn. of American Cancer Institutes believes public awareness of the latest developments in prevention, early detection, treatment, and rehabilitation are critical to the promotion of optimal individual choices. Cancer Information Service at cancer centers provide this awareness to the public, physicians, and allied health personnel.

▶ Guaranteed access to 'state of the art' as well as the 'latest research' techniques at the nation's cancer centers should be preserved. The nation's cancer centers should be identified as centers of excellence and places where patients are referred for state of the art prevention, diagnosis, and treatment.

▶ Quality care and future improvements in management are the products of clinical trials and technology assessment research conducted at cancer centers.

▶ Cancer centers provide leadership in the training of physicians, laboratory investigators, and allied health personnel in an environment which fosters the multidisciplinary development of new methods of cancer diagnosis, prevention, and treatment.

"The AACI would ask that the development of new health care initiatives, recognition of these important past contributions be sustained through the implementation of appropriate statutes and regulations governing the reimbursement of quality cancer care.

▶ The basic benefits package should cover cancer detection, diagnosis and treatment of cancer patients enrolled in qualified clinical trials conducted at or in cooperation with cancer centers.

▶ That reimbursement regulations provide plans for the support and study of technology, outcomes research and practice guidelines emanating from clinical research results.

▶ Cancer centers provide a network for the study

of investigational drugs, the regional supervision of 'off-label' use of drugs and as advisors to regional agencies charged with individual reimbursement decisions.

▶ Cancer centers be recognized as training centers for all types of health care professionals in oncology and reimbursement for this effort be considered. Properly trained personnel in oncology contribute to the quality of care."

NIH Alternative Medicine Office Releases RFA For Grant Awards

The NIH Office of Alternative Medicine has issued its first Request for Applications to fund grants in alternative medicine.

The RFA has been controversial because is does not emphasize "curative" alternative approaches in major diseases such as cancer, and because the concept for the RFA was not reviewed by a chartered advisory committee, but by an ad hoc group of advisors (**The Cancer Letter**, Feb. 26).

Following is the text of the RFA:

RFA OD-93-002
Title: **Exploratory grants for alternative medicine**
Letter of Intent Receipt Date: April 30
Application Receipt Date: June 8

The Office of Alternative Medicine (OAM) was initiated within the Office of the Director (OD), NIH, in response to Congressional language that accompanied the fiscal year 1992 Labor, HHS, and Education and Related Agencies Appropriation Bill in October 1991. The mandate of the OAM is to evaluate what was then termed "unconventional medical practices," and was renamed more recently "Alternative Medicine." The purpose of the OAM is to encourage the investigation of alternative medical practices, with the ultimate goal of integrating validated alternative medical practices with current conventional medical procedures.

The purpose of this Request for Applications is to solicit applications for support of: 1) developing collaborations between practitioners of alternative medicine and conventional researchers; and 2) small scale studies designed to obtain preliminary data relevant to the evaluation of alternative medicine which, for the purpose of this RFA, is understood as a new and unique activity, not currently supported by NIH.

It is anticipated that activities supported by these exploratory grants will form the basis for competitive applications that could be submitted in response to future RFAs, including a Cooperative Agreement RFA, from the Office of Alternative Medicine.

Applications may be submitted by domestic, foreign, for-profit and non-profit organizations, public and private such as universities, colleges, hospitals, laboratories, units of State and local governments, federally recognized Indian Tribal governments, and eligible agencies of the Federal government. Applications from minority individuals and women are encouraged. The OAM encourages non-institution-affiliated individual alternative health care providers/scientists to apply.

Support of projects will be through the NIH Exploratory/Development Grant (R21). Applicants will be responsible for the planning, direction, and execution of the proposed project. The total project period for applications submitted in response to the present RFA may not exceed one year. The anticipated award date is September 30, 1993.

Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also.

The present RFA is a one-time solicitation, and approximately $600,000 total costs is committed to fund applications. Approximately 20 awards, not to exceed $30,000 total costs each, will be made for a period of funding not to exceed 12 months. This funding level is dependent on the receipt of applications of high scientific merit and the availability of funds for this purpose.

Research Objectives: In a recent article, the demographics, prevalence, and patterns of use of unconventional medicine in the United States were described (Eisenberg D. et al, New England J. Med. 328:246-252, 1993). The most relevant findings were: (a) most people used unconventional therapies for chronic rather than life-threatening medical conditions; (b) 72 percent of the respondents who used unconventional therapy did not inform their medical doctor; extrapolation to the United States population suggested that in 1990, Americans made approximately 425 million visits to providers of unconventional therapy; and (c) expenditures associated with this type of therapy appeared to be similar to non-reimbursed expenses incurred for all hospitalizations in the United States. These findings clearly demonstrated that unconventional medicine plays a significant role in the health care system within the United States.

Despite the large number of people using alternative medicine treatments, relatively little scientific data are available to demonstrate convincingly whether or not a particular treatment is safe, efficacious, beneficial, helpful, or leads to a positive outcome (e.g., produces a regression in the size of a tumor, prolongs or improves quality of life, reduces or eliminates adverse symptoms of a toxic treatment). This, in essence, was also the conclusion reached in 1990, in a report published by the Office of Technology Assessment concerning unconventional cancer treatments: "For none of the treatments reviewed in this report did the evidence support a finding of obvious, dramatic benefit that would obviate the need for formal evaluation to determine effectiveness" (U.S. Congress, Office of Technology Assessment, OTA-H-405, 1990, p. 225). The report went on to urge a more systematic analysis of unconventional treatments on major diseases and effect on wellness. These exploratory grants will provide funds to initiate the first stages of systematic evaluation of alternative treatments.

Goals and Scope of the present RFA: This RFA will create a research opportunity for alternative health care practitioners, otherwise unlikely to participate in NIH programs, to contribute to the nation's biomedical effort. These grants will provide funds for initiating short-term studies that are preliminary in nature.

Alternative health care providers and scientists are invited to respond to this RFA to: 1) develop collaborative arrangements (alternative health care providers with experienced scientists, and conversely); and 2) obtain/refine

preliminary data that could form the basis for future applications for larger studies that will investigate and evaluate alternative treatments, utilizing a rigorous, scientific methodological approach. Although it is anticipated that pilot clinical studies of alternative medicine will be the focus of this RFA, laboratory proposals clearly relevant to alternative medicine will also be considered.

Types of interventions to be investigated could include, but are not limited to:

--Diet, nutrition, and lifestyle changes. For example, macrobiotics, megavitamins, diets, and changes in lifestyle.

--Mind/body control. Examples include art therapy/relaxation, biofeedback, counseling, guided imagery, hypnotherapy, and sound/music therapy.

--Traditional and ethnomedicine. For example, acupuncture, Ayur Veda, herbal medicine, homeopathic medicine, Native American medicine, natural products, and Traditional Oriental Medicine.

--Structural manipulations and energetic therapies. Examples are acupressure, chiropractic medicine, massage, reflexology, rolfing, therapeutic touch, Qi Gong.

--Pharmacological and biological treatments. Examples include anti-oxidants, cell treatment, chelation therapy, metabolic therapy, and oxidizing agents.

--Bioelectromagnetic applications. Examples include diagnostic and therapeutic applications of electromagnetic fields (e.g., transcranial electrostimulation, neuromagnetic stimulation, electroacupuncture).

NIH currently supports research projects falling under some of the above headings. Thus, in applications dealing with such topics, the applicants should carefully justify why they consider their proposals to be "alternative."

It is anticipated that the proposed studies will be designed to contribute to the evaluation of the potential for any of these procedures to affect the clinical course and outcome of an illness, and/or to increase wellness. The study of effects of alternative treatment on any major health condition (e.g., cancer, AIDS, hypertension) is encouraged, although any health issue or disease could be the subject of research, if a sound rationale is provided.

For funded applications, the first part of the project will be to develop/finalize the terms of collaboration and, when applicable, to obtain proper approval for the use of human subjects. This part of the project should be completed within approximately three months. To facilitate this important aspect of the grant activity, the OAM may convene two meetings of all grantees; the first shortly after funding and a second meeting approximately three months later.

The acquisition of preliminary data should begin as soon as appropriate collaborations are in place. In instances where collaborations are already in place at the time of funding, the acquisition of data should begin immediately after funding.

Special Requirements: As indicated above, one of the major purposes of this RFA is to foster collaborations between practitioners of alternative medicine and individuals familiar with conventional research methodologies. The requirement for collaboration between alternative medical practitioners and conventional investigators is three-fold: 1) to ensure that experience in research design and statistics, access to patient populations of special interest, and methods of documentation are included in each funded proposal; 2) conversely, to ensure that appropriate expertise in alternative medicine will be available so that research protocols are compatible with the paradigm to be tested (e.g., appropriate choice of treatment or controls, in the context of homeopathy, acupuncture); and 3) to provide a basis for scientific collaboration and better understanding of issues involved in the practice of alternative medicine, as well as conventional biomedical research.

Alternative medical practitioners must provide credible preliminary evidence (e.g., proof of prior collaboration or detailed letter of intent to collaborate) from experienced investigators indicating their willingness to participate in the preliminary studies.

Conversely, institution-based (e.g., university) investigators must provide similar evidence of collaborations with non-university-based alternative health care providers/scientists with training and experience relevant to aspects of the research proposal. It is expected that such arrangements will not merely be pro forma, but rather will be genuine collaborations in which alternative medical practitioners will have significant roles in the development of the protocols, the conduct of the studies, and will be given the opportunity for receiving significant exposure to, and experience in, sound research methodologies.

A research project grant may be made to a non-affiliated individual in the United States rather than to an institution or organization. In such cases, special administrative features pertain.

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

Review Criteria for this RFA will be:

--relevance to alternative medicine;

--scientific and technical merit: proper justification of endpoints; appropriateness of the experimental approach and methodology to test the paradigm to be evaluated (e.g., individualization of treatment, statistical methods allowing for potentially inherent experimental variability);

--medical significance and originality of proposed research;

--qualifications and clinical/research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

--documented intent to develop collaboration(s) that will provide the range of expertise needed for a successful study (proof of collaboration or detailed letter of intent to collaborate); --availability of sound literature documentation or the availability of preliminary data justifying the proposed model to be studied;

--availability of the resources necessary to perform the research;

--appropriateness of the proposed budget.

Inquiries and letter of intent are to be directed to: Dr. Daniel Eskinazi, Office of Alternative Medicine, NIH, Bldg 31 Rm B1-C35, Bethesda, MD 20892; Tel. 301/402-2466; fax 301/402-4741.