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U.S. Radiologists Criticize Canadian Study Of Mammography Screening Showing No Benefit

A Canadian study published this month concludes that mammography screening does not reduce breast cancer mortality in women under age 50, but American radiologists criticized the methods used by the Canadian investigators to reach that finding, and U.S. health agencies stood by their recommendation that women over age 40 should have regular mammograms.

The National Breast Screening Study of Canada found no evidence of reduced mortality after seven years of follow up among women 40-49

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In Brief

ASTRO Elects New Officers; ASSIST Coordinators Express Concern Over NCI Plan To Cut Budget

NEW OFFICERS of the American Society for Therapeutic Radiology and Oncology were elected prior to the society's annual meeting earlier this month in San Diego. The new officers are: chairman of the board of directors, **Sarah Donaldson**, Standford Univ.; president, **J. Frank Wilson**, Medical College of Wisconsin; president-elect, **Lester Peters**, M.D. Anderson Cancer Center; treasurer, **David Hussey**, Hospitals and Clinics, Iowa City; secretary, **Eric Hall**, Columbia Univ. ASTRO awarded its gold medal for distinguished and extraordinary service to the society to **Carlos Perez**, director of the radiation oncology center at Mallinckrodt Institute of Radiology, Washington Univ. School of Medicine, St. Louis; and to **Eleanor Montague**, professor emeritus of radiotherapy, M.D. Anderson. . . . **COORDINATING COMMITTEE** for the American Stop Smoking Intervention Study (ASSIST) met in Washington this month. One item discussed was NCI's plan to cut $5 million from the trial's budget this year, a 20 percent reduction (**The Cancer Letter**, Nov. 6). "We would ask, is this a retreat from NCI's own Year 200 goals?" **Randy Schwartz**, director of the health promotion and education division of the Maine Bureau of Health, and ASSIST project director in that state, said to **The Cancer Letter**. "The goal was a 43 percent reduction in smoking prevalence. Will that goal be cut by 20 percent? It will certainly affect outreach and delivery of tobacco control interventions, though how it would affect each site would be different." . . . **JOHN HANSON**, medical director of the immunotherapy program at St. Luke's Medical Center in Milwaukee, has accepted a $1 million endowment from the William G. Schuett family and Security Bank for expansion of the immunotherapy laboratory and development of a gene therapy laboratory.

Canadian Study Prompts U.S. To Review Mammography Advice

(Continued from page 1)

who were screened annually for five years using clinical breast examination and mammography, compared to a control group that received only breast examination on the first visit.

The trial was designed specifically to determine whether screening women aged 40-49 is effective in reducing mortality, and whether mammography and breast examination together were better than breast examination alone in screening women aged 50-59. So far, mortality in the older age group was not reduced by annual screening for five years, though that result is expected to change over the next few years as longer follow up time is achieved.

The study was published in the Canadian Medical Assn. Journal earlier this month by Anthony Miller and Cornelia Baines, of the Univ. of Toronto.

The study prompted NCI, the Centers for Disease Control, and the Food & Drug Administration to review the screening advice they have given U.S. women since the 1980s. NCI will host a conference Feb. 24-25 to evaluate data from screening trials worldwide.

The U.S. agencies say women should continue to follow the screening recommendations of NCI and the American Cancer Society until the Canadian results are analyzed in relation to other studies. ACS plans to hold a meeting Feb. 1-2 on the breast cancer screening guidelines endorsed by 11 national organizations in 1989.

ACR Criticizes Poor Mammography Quality

The American College of Radiology issued an eight-page statement, "A Critical Review," in response to the study. The statement was written by Stephen Feig, Thomas Jefferson Univ. Hospital, Philadelphia, and Daniel Kopans, Massachusetts General Hospital. The two American radiologists have criticized the Canadian study for several years, and both served as advisors to the trial. Feig resigned his advisory position in protest in 1984.

"Several major flaws in the design and performance of the trial have seriously compromised the results," Feig and Kopans wrote. Their main criticisms, with comment by Baines, deputy director of the study, follows. Miller, the lead author on the study, was traveling and unavailable for comment.

▶**Mammographic quality:** The 15 screening centers used any existing mammographic equipment and made no attempt to improve the quality of mammography, Feig and Kopans wrote. Technical quality standards were not enforced, the dose for each mammogram was kept low at the expense of image quality, and there was no special training for the technologists and radiologists. "Thus, instead of evaluating the efficacy of high quality mammography for screening, the trial could only test the validity of mammographic screening as it was then being generally practiced at the time the study was forming."

An independent review of the Canadian mammograms, published in 1990, said that in the first four years of the trial, more than 50 percent of the mammograms were "poor or completely unacceptable." Feig and Kopans said the quality improved over time, but should have been higher from the start.

Baines said to **The Cancer Letter** that the American consultants used standards of the mid-1980s to evaluate mammograms taken in 1980. Major technical improvements took place in those few years.

Specifically, the Americans gave low scores to mammograms using the straight mediolateral view rather than the mediolateral oblique view, a technical advance that occurred in the early 1980s which improves the image of the tail of the breast.

"As soon as it was feasible, we switched to the oblique view," after the first round of mammograms was completed in 1985, Baines said. "If you want to have an objective assessment of mammograms, you don't penalize them for what was not being done."

Baines said she re-evaluated the images, using the strict standards the consultants used, but deleting the bad score given to the straight views simply because they were not oblique. "When you delete those scores, you end up with more than 85 percent achieving the quality standard they set up," she said.

▶**Randomization process:** More advanced cancers were found in the screened group in the first round of screening than in the control group, according to

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Feig and Kopans. "This means that either by chance or through a flaw in the randomization process, more women with prognostically poor tumors were placed in the study group. Mammographic screening is effective because it can detect cancers at a smaller size and earlier stage than physical examination. If cancers are at a later stage at the outset, the mammography will have little or no influence on mortality. With more advanced cancers placed in the study group, more deaths from cancer would be expected among these women a priori."

Said Baines: "That is absolutely unfounded, there is no evidence for that and it is quite astonishing that two people of their standing would say that."

The randomization was "meticulous," Baines said. All variables were matched across the arms by the randomization.

"If anything would cause subversion, it would be family history of breast cancer and lumps," she said. "Those are equally distributed." She noted that a study by a prominent American radiologist, Lazlo Tabar, also had more cancers in the screened group.

▶**Inconsistent intervention:** Biopsy recommendations were not always followed, Feig and Kopans wrote. If a mammogram was interpreted as positive, the woman was referred to a surgeon who determined whether a biopsy was needed, but the surgeons had not agreed upon guidelines, they said. In about 25 percent of the cases, a biopsy was not performed when recommended by the surgeon.

Biopsy recommendations "were not always followed, but the biopsy rates we produced were good enough to detect cancers," Baines said. "Our cancer detection rates were excellent."

▶**False reassurance:** If the screening was ineffective, there should be the same number of deaths in each arm of the study, Feig and Kopans said. Since there were more deaths in the screening group, diagnosis must have been delayed. This could have been "the result of women being falsely reassured from a negative screening study," who then discounted any problem she may have discovered in her breast between screenings, they said. In contrast, a woman in the control group who detected a problem "would have no similar false reassurance and would be more likely to seek immediate evaluation." Thus, the screened woman would be more likely to present with cancer at a later stage. The delay in diagnosis could be the reason for some of the excess mortality in the screened group, they said.

Baines said the study's rate of interval cancers--the cancers that occur between screenings--was not high, indicating that screening quality was good, Baines said.

Seven-year survival in the Canadian study for women age 40-49 is 95 percent, Baines noted. "If our mammography is so bad, how is it that we have good survival and low interval cancer rates?"

Two other American screening experts, Charles Smart and Curtis Mettlin, have prepared a review of the study that is scheduled for presentation to the ACS Breast Cancer Task Force next week.

Mettlin said he had three concerns: the lenght of followup and relatively small number of deaths among the younger women; whether the cohorts were truly at equal risk of breast cancer death at the outset; and concerns about the quality of the screening process, particularly the mammography in the early years of the study.

Baines responds to criticism of the Canadian study in an article in the winter 1992 "Women's Health Issues," published by the Jacobs Institute of Women's Health.

Study Is 'Politically Incorrect'

"Undermining belief in the effectiveness of screening women 40-49 appears to be politically incorrect," Baines writes in the WHI article. "It is not hard to find other studies whose results have also been politically incorrect and whose investigators have been criticized. It is that science is antiauthoritarian? Belief systems are not easily relinquished."

In a press release, NCI refused to join in the fracas, saying, "Experts need to analyze the Canadian results in the context of the large body of knowledge generated by other studies completed in the United States and Europe. The analysis is necessary to determine the implications of these results for breast cancer screening guidelines."

Evidence in support of the guidelines is strongest for women over age 50, showing a 30 percent mortality reduction in women who follow the advice, according to the NCI statement. No definitive data exists in support of screening for women age 40-49 because studies have not included enough women in this age group, NCI said.

The two major American studies are the 1960s Health Insurance Plan of New York randomized controlled trial that demonstrated a 30 percent reduction in breast cancer mortality for women screened by mammography and breast examination, but did not determine the effect of screening for women under age 50. The 1970s Breast Cancer Detection Demonstration Project demonstrated that mammography can detect cancers at a smaller size and earlier stage than clinical examination, but the study was not randomized.

Until the February conference, NCI and CDC

advised women to continue to follow the existing U.S. guidelines on breast cancer screening, which state:

▶Clinical examination of the breasts and mammography are the basic detection methods. The examinations are complementary and both are necessary to achieve maximum detection rates.

▶The screening process should begin by age 40 and consist of an annual clinical breast examination with screening mammography performed at one- to two-year intervals.

▶Beginning at age 50, both clinical breast examination and mammography should be performed annually.

▶Women should be encouraged to do monthly breast self examination.

▶Special surveillance be given women with a personal history of breast cancer or history of breast cancer in a mother or sister.

ODAC Advises Tamoxifen Approval In Metastatic Male Breast Cancer

FDA's Oncologic Drugs Advisory Committee recommended the approval of tamoxifen for the treatment of metastatic breast cancer in men.

At its meeting earlier this month, the committee voted 10 in favor, with one abstention, for approval of the supplemental New Drug Application submitted by ICI Pharmaceuticals for Nolvadex.

Male breast cancer is uncommon, with only 1,000 new cases diagnosed each year in the U.S. Though there is little data on the rare cancer, it is believed to have similar risk factors as female breast cancer, and estrogen is believed to play a significant role, according to Aman Buzdar, M.D. Anderson Cancer Center, who presented data to the committee.

Five year survival of node negative male breast cancer is 57 to 90 percent, while survival of node positive cancer is 28 to 57 percent. Treatment is modified radical mastectomy, though lumpectomy and axillary dissection is done if a patient is unable to undergo extensive surgery. The majority of cases (84 percent) are estrogen receptor positive.

Treatment of metastatic male breast cancer involves hormonal therapy or ablative hormonal therapy such as orchiectomy, adrenalectomy, or hypophysectomy.

The data for tamoxifen for treatment of male breast cancer is based on small studies in the literature and case reports. Ian Jackson of ICI presented data on 132 evaluable patients, from 20 investigators, included in three publications.

Jackson said tamoxifen resulted in a 50 percent response rate in 66 patients as treatment of metastatic breast cancer.

As an adjuvant therapy, Jackson said tamoxifen resulted in a 61 percent response rate, compared to 44 percent for historical controls.

In its discussion, the committee noted that the data on tamoxifen in men as presented was limited, but made its decision based partly on the extensive data on tamoxifen in women.

"This is an example of clinical experience getting ahead of the published data," committee member Harold Harvey said. "As clinicans we think we know how to treat male breast cancer, based on our experience with women. I am persuaded that the disease is the same in men as in women."

However, the committee voted unanimously against approval of tamoxifen for delaying recurrence following mastectomy and breast irradiation in men with axillary node positive breast cancer, citing insuffient data.

The one absention from the vote for approval of tamoxifen as treatment was Steven Piantadosi, who said the quality of the data "was among the worst I have seen."

On the second day of the meeting, the committee was scheduled to hear a presentation for a New Drug Application for perfosfamide (Pergamid), by Scios Nova Inc., for ex vivo purging of bone marrow of patients with acute myelocytic leukemia. However, the Parklawn Building in Rockville, MD, FDA headquarters, was closed due to a water main break. The presentation had not been rescheduled as of this writing.

NCI Advisory Group, Other Cancer Meetings For Dec., Jan., Future

American Society of Hematology Annual Meeting--Dec. 4-8, Anaheim, CA. Contact ASH, 202/857-1118.

Research Opportunities in Biomolecular Engineering--Dec. 7-8, Omni Shoreham Hotel, Washington DC. Contact Ann Dieffenbach, phone 301/496-7301.

San Antonio Breast Cancer Symposium--Dec. 9-10, San Antonio, TX. Contact Lois Dunnington, symposium coordinator, 512/567-4745.

American Endocurietherapy Society Mid-Winter Meeting--Dec. 9-12, Beaver Creek, CO. Contact AES, phone 215/574-3158.

National Cancer Advisory Board--Dec. 14-15, NIH Bldg. 31 Conference Room 10, open 8 a.m.-adjournment.

NCAB Committee on Interactions with Voluntary Organizations--Dec. 14, NIH Bldg. 31 Conf. Rm 8, open 3:30 p.m.-adjournment.

NCAB Committee on Cancer Centers--Dec. 14, NIH Bldg. 31 Conf. Rm 9, open 5 p.m.-adjournment.

Cancer Biology and Immunology Contracts Review Subcommittee C--Dec. 16-18, Bethesda Ramada Inn, Bethesda, MD, open 8:30-9:30 a.m.

President's Cancer Panel Special Commission on Breast Cancer--Jan. 11-12, Atlanta, GA. Hyatt Atlanta Airport. Topic: Treatment, rehabilitation and quality of life for women with breast cancer.

Breast Cancer in Premenopausal Women--Jan. 13-14, Bethesda, MD, NIH Masur Auditorium. Contact Dr. Edward Trimble, 301/496-2522.

Developmental Therapeutics Contracts Review Committee--Jan. 15, Bethesda Holiday Inn, Bethesda, MD, open 9-10 a.m.

Radiation Therapy Oncology Group Semi-Annual Meeting--Jan. 15-17, New Orleans, LA. Contact Nancy Smith, RTOG, phone 215/574-3205.

Specific Immunotherapy of Cancer with Vaccines--Jan 21-14, 1993, Washington, DC. Contact Conference Dept., New York Academy of Sciences, phone 212/838-0230.

Queen's Cancer Institute Symposium on Women and Cancer--Jan. 27-29, Honolulu, HI. Contact Grace Iwahashi, Queen's Medical Center Cancer Institute, 1301 Punchbowl St., Honolulu, HI 96813, phone 808/547-4660, fax 808/537-7819.

National Biotherapy Study Group Nursing Biotherapy Symposium--Jan. 27-28, San Diego, CA. Contact NBSG Central Office, phone 615/791-6393.

Future Meetings

The Role of Toxicologic Pathology in Safety Assessment--Feb. 9-10, Washington, DC. Contact Sharon Holzmann, National Academy of Sciences, phone 202/334-1553.

Grant Proposal Writing Seminar--Feb. 22-26, Chicago. Contact Mary Kearney, American College of Surgeons, phone 312/664-4050.

Breast Cancer Research: Current Issues, Future Directions--April 25-28, Atlanta, GA. Contact Continuing Medical Education, Emory Univ. School of Medicine, 1440 Clifton Rd NE 107 WHSCAB, Atlanta, GA 30322, fax 404/727-5667.

Loss of Genomic Integrity in Neoplasia--April 21-23, Chapel Hill, NC. Contact Vickie McNeil, UNC Lineberger Comprehensive Cancer Center, phone 919/966-3036.

American Radium Society Annual Meeting--April 24-28, Aruba. Contact Office of the Secretariat, phone 215/574-3179.

Administrators in Oncology/Hematology Assembly--May 6-8, Nashville, TN. Contact W. Robert Cooper, phone 309/672-5681.

Robert Wood Johnson Foundation Call For Proposals: Tobacco Policy

The Robert Wood Johnson Foundation is requesting proposals for research and evaluation projects that will produce policy-relevant information about ways to reduce tobacco use in the U.S.

Up to $5 million will be available for the program, which is intended to encourage experts in political science, public health, law, economics, and other behavioral and policy sciences to address issues related to tobacco use.

Following is the text of the call for proposals:

The Tobacco Policy Research and Evaluation Program is intended to help identify, analyze, and evaluate public and private sector policies aimed at reducing tobacco use (including snuff and chewing tobacco). Research projects may address policies at the national, state, or local levels in the public sector, or they may address private sector policies within companies, associations, unions or trade groups. Projects analyzing policies affecting children and youth are especially encouraged. Since the focus of this program is the United States, studies of policies in other countries will be considered only to the extent they may directly inform U.S. policy.

Examples of the types of issues that would be of interest under the program include:

--the ways that various means of limiting access to tobacco products affect initiation and prevalence of use among youth.

--the costs and benefits of policies or ordinances intended to restrict smoking or protect nonsmokers.

--the impact of tobacco product taxes on use.

--the likely consequences--intended and unintended--of new efforts to regulate tobacco products.

--the ways such policies are diffused.

--the impact of advertising and promotion strategies on the initiation and use of tobacco products.

Preference will be given to applicatins that are tax exempt under Section 501(c)(3) of the Internal Revenue Code and are not private foundations as defined under Section 509(a).

To be considered favorably under this solicitation, proposals must demonstrate the potential to produce new information directly relevant to policies intended to reduce tobacco use....

Grant funding amounts and time periods are flexible and will be commensurate with the size and scope of the proposed activity. Awards are expected to range from $50,000 to $350,000 and may extend up to three years.

Letters of intent are due Jan. 15. Inquiries may be directed to Dolores Colello, Program Assistant, Robert Wood Johnson Foundation, Route 1 and College Road East, PO Box 2316, Princeton, NJ 08543-2316; phone 609/243-5961.

RFPs Available

RFP NIAID-DAIDS-93-18

Title: Laboratory for assessment of mucosal immune responses induced by AIDS vaccines in clinical trial volunteers

Deadline: Approximately Jan. 5

The National Institute of Allergy and Infectious Diseases has a requirement to provide for the centralized performance of immunological assays to evaluate HIV-specific humoral and cellular mucosal immune responses in support of clinical trials of prototype AIDS vaccines. The purpose of this contract is to support the NIAID in its mission to stimulate research towards discovery and testing of prototype vaccines for the acquired immunodeficiency syndrome (AIDS).

NIAID requires a Mucosal Immunology Laboratory to evaluate

reproductive tract, gut, blood, and other mucosal specimens from vaccine clinical trial volunteers for humoral and cellular mucosal immune responses induced by immunization with prototype AIDS vaccines. This effort will support the research of AIDS investigators, including the AIDS Vaccine Evaluation Group, the National Cooperative Vaccine Evaluation Groups, and other programs initiated by NIAID.

Specifically, the selected Contractor shall be responsible for: 1) performing specific immunological assays for detection of HIV-specific antibody and cellular responses in mucosal site and blood specimens from AIDS vaccine recipients; 2) developing standard protocols for the collection, processing, and storage of mucosal specimens at the vaccine trial sites; 3) receiving, cataloging, tracking, coding, storing, and maintaining an inventory of vaccinee specimens arriving for evaluation; and 4) maintaining a test result database and transferring data electronically to the AIDS Vaccine Clinical Trials Network Data Coordinating and Analysis Center (DCAC).

Requests for the RFP may be directed in writing to (provide three self-addressed mailing labels): Lawrence Butler, Contracting Officer, Contract Management Branch, NIAID, Solar Bldg, Rm 3C-07, 6003 Executive Blvd, Bethesda, MD 20892.

RFP NIAID-DAIDS-93-19

Title: biochemical screens for agents effective against AIDS-related opportunistic infection

Deadline: Approximately Jan. 5

The Developmental Therapeutics Branch, Basic Research and Development Program, Division of AIDS, NIAID, has a requirement to apply established biochemically-based enzymatic or non-enzymatic assays to screen agents for inhibition of one or more steps in the metabolism of AIDS-associated opportunistic pathogens. These biochemical prescreens are considered particularly useful for rapid testing of compounds.

Examples of such assays may include, but not be limited to: protein synthesis, dihydrofolate reductase, and dihydropteroate synthase. The major effort of this contract will involve the screening of a large number of compounds. A secondary focus of this contract will be development/modification of automated biochemical assays and their application to drug testing against opportunistic infections in AIDS.

It is anticipated that some assays will require isolation of enzymes from relevant microorganisms or cloning to obtain the protein. However, most of the enzymes and recombinant proteins required for the development of assays in this project will be provided by the AIDS Reference and Reagent Repository. Other non-enzymatic assays may be developed /used to evaluate drug activities in vitro. At the present time, NIAID has one contract that is scheduled to end in 1993 to screen agents in enzymatic assays.

This project will take approximately three years to complete. A level-of-effort, cost reimbursement contract is anticipated.

Requests for the RFP may be directed in writing to (provide three self-addressed mailing labels): Cyndie Cotter, Contract Management Branch, NIAID, Solar Bldg, Rm 3C07, 6003 Executive Blvd, Bethesda, MD 20892.

RFP NIAID-DAIDS-93-22

Title: genetic sequence variability of HIV-1 and related lentiviruses

Deadline: Approximately Jan. 5

The National Institute of Allergy and Infectious Diseases has a requirement for a contractor to receive samples infected with HIV-1 or related lentiviruses, to amplify virus-specific genetic sequences from these samples, and to clone and sequence these amplified fragments. The Contractor will be required to design gene amplification primers for distinct regions of the virus genome and for diverse viral isolates. The Contractor will be required to amplify and clone sizable genomic fragments (>1500 base pairs), and carry out large-scale genetic sequencing (approximately 200,000 bases/year).

Specifically, the selected contractor shall be responsible for: 1) amplifying, cloning and sequencing HIV-1 and related lentivirus-specific gene fragments from samples derived from HIV-infected individuals provided through the Project Officer; 2) compiling and analyzing genetic sequence data, and transferring data to the HIV Genetic Sequence Database and Analysis Unit at the Los Alamos National Laboratory; 3) receiving, cataloging, processing, storing samples, and distributing samples to other investigators; and 4) providing an Inventory and Database Management System.

Requests for the RFP are to be directed in writing to (provide three self-addressed mailing labels): Kristiane Hofacker, Contract Specialist, Contract Management Branch, NIAID, Solar Bldg, Rm 3C07, Bethesda, MD 20892.

RFAs Available

RFA AI-92-12

Title: **Women's interagency HIV study**

Letter of Intent Receipt Date: Jan. 11

Application Receipt Date: Feb. 18

The Vaccine Trials and Epidemiology Branch of the Div. of AIDS, National Institute of Allergy and Infectious Diseases, invites applications for cooperative agreements for the establishment of a Women's Interagency HIV Study (WIHS) to investigate the clinical, laboratory, and psychosocial impact of HIV infection in women. The WIHS will use a multi-site, prospective study design to gather data on the clinical, immunological, virological, and behavioral aspects of HIV infection and disease in women. This study will investigate the full spectrum of clinical disease caused by HIV infection in women. It also will seek to determine other cofactors that may be associated with HIV disease progression in women.

Applications may be submitted by domestic non-profit, and for-profit research institutions; public and private organizations. Applicants must demonstrate the capability to recruit and maintain a minimum of 300 HIV-seropositive women and 75 HIV-seronegative women who engage in activities that put them at high risk of acquiring HIV infection; the proposed study population should reflect the socioeconomic, racial, and ethnic female populations infected with HIV.

Applications funded under this RFA will be supported through the NIH cooperative agreement (U01). Approximately $5 million will be available for the total costs of the WIHS during its initial year. The earliest possible award date is July, 1993. NIAID anticipates making two to five awards.

The primary purpose of this RFA is to develop a cooperative multi-site prospective epidemiologic study of the clinical, immunologic, and virologic and behaviorally-associated aspects of HIV disease progression in women. The CDC and NIAID have initiated the initial phase of this interagency prospective study of HIV-infected and uninfected women through the CDC's 1991 program announcement No. 115 (see Federal Register, vol. 56, no. 65, Thursday, April 4, 1991), the HIV Epidemiology Research Study (HERS). The data collection instruments (medical history intake questionnaires, physical exam protocols, and laboratory specimen collection forms) for this phase of the study are being developed collaboratively between the CDC, NIAID, the four currently funded clinical sites, and an interim data center. The data collection instruments developed for the HERS are available on request by faxing request to Dr. Sandra Melnick at (301) 402-1506. When new sites are awarded under this RFA awardees will collaborate with the investigators from the CDC HERS sites

to review the study data collection instruments and physical examination protocols, to arrive at compatible data collection procedures.

Inquiries and letter of intent may be sent to Dr. Sandra Melnick, Vaccine Trials and Epidemiology Branch, Div. of AIDS, NIAID, Solar Bldg, Rm 2A28, 6003 Executive Blvd, Bethesda, MD 20892.

RFA CA-93-03

Title: Therapeutic studies of primary central nervous system malignancies in adults

Letter of Intent Receipt Date: Jan. 15

Application Receipt Date: March 10

The Cancer Therapy Evaluation Program and the Radiation Research Program of NCI's Div. of Cancer Treatment invite applications for cooperative agreements (U01) from consortia of institutions to perform Phase I and II clinical evaluations of promising new chemotherapeutic or biologic agents for the treatment of primary central nervous system (CNS) malignancies and to perform ancillary laboratory studies of aspects of CNS tumor biology with potential clinical implications. Integrated packages of individual applications are encouraged, with the lead institution of a proposed consortium indicating which participating institutions will provide organizational support, scientific leadership, laboratory capabilities, and/or patient resources. Each consortium of institutions will be referred to as a CNS Consortium (CNSC) for the purpose of this RFA.

Applications may be submitted by North American non-profit and for-profit organizations, public and private. It is essential that applications be submitted as an integrated package from a team or consortium (CNSC) of medical institutions (a minimum of three) that agree to work together with a single Project Leader and a single administration, and submit applications that will be reviewed in relation to the consortium. Together, the institutions in the consortium would encompass experience in investigational drug clinical trials, access to sufficient numbers of primary CNS tumor patients to enter a minimum of 60-80 fully evaluable cases per year onto Phase I and II protocols, expertise in laboratory investigation of the biology of human gliomas, and access to a Central Operations Office for coordination of research activities and data analysis. Except under unusual circumstances, the Central Operations Office/Coordinating Center would be expected to reside at the Project Leader's institution.

Approximately $1,500,000 in total costs per year for four years will be committed to specifically fund applications submitted in response to this RFA. It is anticipated that six to nine individual awards will be made to one to three consortia. The total project period may not exceed four years.

The primary goal of this initiative is to stimulate clinical research in the treatment of primary CNS malignancies in adult patients by providing support for consortia of institutions to perform Phase I and II clinical evaluations of promising new chemotherapeutic or biologic agents. A secondary goal is to utilize the consortia as a mechanism for sharing human brain tumor specimens among investigators conducting laboratory studies relevant to the biology, clinical behavior, or therapy of CNS tumors, particularly malignant gliomas.

Clinical trials will take advantage of new developments in drug and radiation resistance, radiation sensitization, biological response modification, immune modulation, induction of apoptosis, differentiation induction, therapeutic irradiation techniques, induction or suppression of specific gene function, or other innovative approaches. Each CNSC will be formed for the purpose of: 1) sharing expertise of researchers in multiple disciplines; (2) conducting joint phase I and II clinical trials to provide adequate patient populations and timely completion; and (3) sharing of tumor specimens and data useful in the conduct of clinical pharmacologic and correlative laboratory studies. Participant institutions in the proposed consortium may be involved in clinical trials and/or laboratory studies.

It is anticipated that one to three consortia will be established, comprising three to nine institutions. Each CNSC will select the specific agents to be tested in accord with their scientific interest and expertise and will develop a series of appropriate Phase II or Phase I trials with supporting protocol documents. Each applicant CNSC should submit as examples one or more draft clinical protocols as supplements to the Central Operations Office/Coordinating Center (Project Leader) and the participant institution applications. The CNSC, with the assistance of the NCI Program Director, will develop a plan for prioritization of investigational trials. NCI may provide NCI-sponsored IND agents or provide assistance to the awardee(s) by sponsoring or cross-referencing INDs for selected agents. Each CNSC must have documented numbers of patients with CNS tumors and a history of accrual of patients to clinical trials adequate for two-six phase I or II trials (60-180 patients) per year.

It is expected that all of the CNSC institutions together will be able to complete approximately six phase I or phase II trials (180 patients) per year. In addition, proposed consortia must have: 1) adequate radiotherapy support for clinical trials utilizing radiation in combination with other modalities; 2) adequate central data collection and processing capabilities as well as biostatistical expertise; 3) adequate pathology support for both institutional tumor classification and central neuropathology review and for banking and distribution of tumor tissues for concurrent and future laboratory studies; 4) mechanisms to collect and store patient specimens for laboratory studies being conducted by institutions in the CNSC; (5) expertise in antineoplastic drug pharmacology/pharmacokinetics.

The correlative laboratory research program in a CNSC should address at least one field of research into the biology of human malignant gliomas with some potential for future clinical relevance. Examples of research fields for laboratory studies include: molecular genetics and cytogenetics, gene function and expression, signal transduction pathways, radiobiology, growth regulation, metabolism, differentiation and gene modulation by investigational agents, intracellular metabolism, mechanisms of drug resistance in tumor cells, CNS pharmacokinetics, invasion and spread, cytokine production or interactions, immune function and antigen expression, or other aspects that may have clinical implications or lead to new therapeutic approaches. Investigators are not limited to the above areas of laboratory experimentation.

Correlative laboratory studies need not be directly related to individual clinical Phase I/II trials but should attempt to utilize the large clinical database that will be generated by the consortium to identify potential correlates of tumor behavior, and laboratory studies should be based on strong and testable hypotheses. A clear rationale should be given for the experimental design and technological methodologies selected. Preliminary data from appropriate tumor models or analysis of patient specimens should be provided to support the feasibility of each study. The laboratory assays must utilize tumor specimens from patients and there should be an established plan for prioritization of specimen distribution to collaborating laboratories. Participating institutions primarily involved in laboratory studies may accrue patients on CNSC clinical trials if the minimum clinical resources are in place.

Inquiries and letter of intent may be directed to:

Dr. Richard Kaplan, Senior Investigator, Cancer Therapy Evaluation Program, National Cancer Institute, Executive Plaza North Rm 734, Bethesda, MD 20892, phone 301/496-8866; fax: 301/480-4663.

RFA CA-93-05
Title: **Research and development projects in chemoprevention**
Letter of Intent Receive Date: Dec. 9
Application Receipt Date: Feb. 9

NCI's Div. of Cancer Prevention and Control invites applications for cooperative agreements to encourage coordinated submissions of related projects from investigators who want to collaborate on studies dedicated to developmental research in chemoprevention.

Applications may be submitted by domestic and foreign for profit and nonprofit organizations, public and private. Each application will be considered on its own merit.

This RFA will use the cooperative agreement (U01). Approximately $4 million in total costs per year for five years will be committed. It is anticipated that nine to 15 awards will be made annually. The total project period should not exceed five years. The earliest feasible start date will be December 1993.

This RFA encourages submissions of applications from investigators wanting to conduct collaborative translational research in cancer chemoprevention. Translational research moves the results of basic research studies in the laboratory or developmental studies to clinical research in human subjects or populations. The research objectives of these projects should be the development of intermediate biomarkers of cancer risk and the evaluation of the efficacy of individual biological and/or molecular markers as intermediate endpoints in chemoprevention trials.

Candidate chemical, biological, molecular, and dietary cancer chemopreventive agents have been identified from in vivo studies in animal model systems, and epidemiological studies. The efficacy of each of these a individually or in concert in modulating cancer risk can best be evaluated through prevention clinical trials. Limitations of the usefulness of such trials is the long duration and large sample populations generally needed to achieve statistical significance. This limitation could be overcome by identification of biological or molecular markers suitable for use as intermediate endpoints in the process of carcinogenesis. Ideally, such markers would be expressed in an abnormal form in tumor tissue or washings or in serum of high-risk individuals, but revert to the normal form when exposed to the chemopreventive agent.

Our evolving understanding of the molecular biology of carcinogenesis has identified possible oncogene and suppressor gene candidates and molecular alterations in these candidates and their interactions with other cellular components, that could serve as intermediate markers in cancer chemoprevention trials. Examples would include sequential genetic alterations in oncogenes HER-2/neu, C-myc, c-abl; in tumor suppressors RB, p53 and APC; markers for increased risk for cancer (Li-Fraumeni-p53, NF-1, APC, and early onset 17q21); and interaction between oncogenes, suppressors RB, p53 genes and the cyclin P34 complex. New developments in the understanding of cellular function and metabolites have provided information on possible candidate markers for cell growth, proliferation, differentiation, and neoplastic transformation. Included among these candidates are abnormal cytology, nuclear aberrations (micronuclei), ornithine decarboxylase and/or prostaglandins synthetase, DNA ploidy, and colonic mucosal proliferation.

Cancer chemoprevention trials responsive to this RFA will examine modulation of candidate markers in respect to administration of chemopreventive agents. Additionally, these markers could be used to identify human populations at high risk for cancer, and therefore useful as sample populations for these trials.

Inquiries may be directed to: Dr. Marjorie Perloff, Chemoprevention Branch, NCI, Executive Plaza North Suite 201, Bethesda, MD 20892-4200, phone 301/496-8563; fax: 301/402-0553.

Program Announcement

PA-93-016
Title: **Molecular and cellular biology of metastatic tumor cells**

NCI invites exploratory/developmental grant applications to study the molecular and cellular biology of metastatic tumor cells. This special initiative is designed to promote collaborations and facilitate scientific interchange between investigators, one with experience in the biology of metastasis and the other in a more basic scientific discipline such as molecular or cellular biology, or biochemistry. Therefore, prospective Principal Investigators need to identify a research collaborator.

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments. Support will be through the NIH exploratory/development research grant (R21). The program provides limited funds for short-term research projects. The direct costs per year for each application funded by NCI must not exceed $50,000. Total project period may not exceed two years.

The goal of this initiative is to provide funds for preliminary research projects that will form the basis of future R01 applications to investigate metastasis. The intent is to (1) foster collaborative research between investigators with basic molecular and cellular biological and biochemical research experience, and those with experience in metastasis research, and (2) increase number of laboratories/investigators addressing metastasis.

The scope of the research may encompass the application of any aspect of molecular and cellular biology and biochemistry to the investigation of metastasis biology. Applications should be for preliminary data gathering or pilot feasibility studies, and should be founded on the combined research experience of the Principal Investigator and his/her collaborator. The application should specifically address how the application meets the intent of the initiative, e.g., the development of a new collaboration between an investigator with basic molecular and cellular biological and biochemical research experience and one with experience in metastasis research. Furthermore, the research collaborator should address how the proposed research will relate to and integrate with other ongoing research in his/her laboratory.

Inquiries may be directed to:

Dr. Suresh Mohla, Chief, Cancer Biology Branch, NCI, Executive Plaza South Rm 630, Bethesda, MD 20892, phone 301/496-7028, fax 301/402-1037.

Cancer Letter Publications Avaialble

A limited number of copies of **The Cancer Letter's** 20th anniversary publication, "The National Cancer Act of 1971: The First 20 Years of the War on Cancer," are still available for $15 each (includes postage and handling).

The document is a year-by-year history of the National Cancer Program, as reported in **The Cancer Letter.** It also contains an index of all articles in the newsletter from 1973-1990.

Also available are copies of the "Annual Index: 1991" to **The Cancer Letter** and **The Clinical Cancer Letter,** for $8 each.

Write, call or fax: **The Cancer Letter,** PO Box 15189, Washington, DC 20003, phone 202/543-7665, fax 202/543-6879.