THE CANCER LETTER

Vol. 20 No. 29
July 22, 1994

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

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

Pitt Inquiry Panel Proceedings Suspended, ORI To Take Over NSABP Investigation

The proceedings of the inquiry panel investigating possible scientific misconduct by three top officials of the National Surgical Adjuvant Breast & Bowel Project were suspended last week, **The Cancer Letter** has learned.

The three members of the inquiry panel as well as Bernard Fisher, Carol Redmond and D. Lawrence Wickerham, the three NSABP officials under inquiry, were notified July 12 that the meeting, scheduled for the following two days, had been suspended.

"We will have further information on this matter in due course," Jane Thompson, acting research integrity officer at the Univ. of Pittsburgh,

(Continued to page 2)

In Brief

Gaus Heads AHCPR; Lineberger Names New Leadership In Oncology And Clinical Research

CLIFTON GAUS has been named administrator of the Agency for Health Care Policy and Research. Gaus worked on the White House health reform proposal as a senior adviser to Assistant Secretary for Health **Philip Lee**. The $154 million agency was created by Congress in 1989. Gaus is a former director of the Center for Health Policy Studies at Georgetown Univ. Medical School. Gaus succeeds **J. Jarrett Clinton**, who was the agency's acting administrator. Clinton has been named regional health administrator in the Atlanta office of the Dept. of Health and Human Services. . . . **LINEBERGER COMPREHENSIVE** Cancer Center, Univ. of North Carolina, has recruited new leadership and reorganized its clinical programs. **Beverly Mitchell** has been named chief of the division of hematology and oncology in the Dept. of Medicine at UNC School of Medicine. She also has been appointed associate director of clinical science of the Lineberger Center. She is the Wellcome Distinguished Professor of Cancer Research, professor of medicine and pharmacology, and serves on the NCI Div. of Cancer Treatment Board of Scientific Counselors. **Joel Tepper** has been named associate director of clinical research and chair of the Protocol Review Committee. He is professor and chair of the department of radiation oncology. **Thomas Shea** has been named director of the Protocol Office and associate chief for clinical research in the Dept. of Medicine's division of hematology and oncology. He is associate professor of medicine and director of the bone marrow transplantation program of UNC Hospitals. . . . "In Brief" is continued to page 6.

ORI, In Turn-Around, To Take Over NSABP Investigation

(Continued from page 1)
wrote in a letter faxed to participants of the proceeding.

Though Pitt officials and others involved in the case declined to comment, citing confidentiality of such proceedings, numerous sources confirmed that the HHS Office of Research Integrity has decided to take the case back from the university.

About-Face For ORI

If the changeover indeed takes place, it would constitute a dramatic about-face for ORI.

Initially, in discussions with the staff of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, ORI officials opposed conducting the inquiry in-house, opting instead to refer the case to Pitt, sources said.

Research integrity inquiries are conducted by HHS grantee institutions, unless there is a compelling reason to question the ability of the institutions to conduct the proceedings.

In investigations where the researchers in question are prominent, institutions can open themselves to accusations of letting their stars off the hook. Alternatively, they can be accused of throwing the book at their researchers, lest there be an appearance of excessively lenient treatment.

Generally, ORI handles no more than one out of five inquiries in-house.

Who is the Client?

In the aftermath of the scientific fraud scandal involving Roger Poisson of St. Luc Hospital, Pitt hired a Washington law firm to represent its own interests as well as those of NSABP chairman Fisher and biostatistician Redmond.

Prior to the first hearing by the Subcommittee on Oversight and Investigations, attorney Martin Michaelson, who was hired by Pitt, accompanied Fisher and Redmond as they were questioned by the subcommittee staff, sources said.

A source who was present at the session said to **The Cancer Letter** that Michaelson did not represent himself as an attorney for either Fisher of Redmond. At that time, asked by **The Cancer Letter**, several senior Pitt officials said Michaelson represented the university.

However, in a suit filed two weeks ago, Fisher claimed that Michaelson gave him a different impression.

"During a meeting on March 23..., Dr. Fisher asked Michaelson if he was 'my attorney,' to which Michaelson responded in the affirmative," Fisher's complaint states.

After ORI mandated an inquiry and delegated it to Pitt, the university's interests had formally diverged from Fisher's and Redmond's.

Subsequently, Fisher's suit alleges, Michaelson stayed on as counsel to the inquiry panel. In that capacity he used Fisher's confidences against him, the complaint says.

Institutional Inquiries of Superstars

Michaelson, a defendant in Fisher's suit, declined to comment on the case. The suit also names Michaelson's Washington law firm, Hogan & Hartson, Pitt chancellor Dennis O'Connor, senior vice chancellor Thomas Detre and NSABP interim chairman Ronald Herberman.

The complaint has been filed in the US District Court for the Western District of Pennsylvania, but the defendants remain to be served, sources said.

Sources familiar with scientific integrity procedure said cases where researchers and their institutions start out as allies and end up adversaries are common in such disputes.

"It's precisely what you want to avoid," a Capitol Hill source said to **The Cancer Letter**. "It seems that ORI has belatedly recognized that institutions are notoriously incapable of conducting inquiries of misconduct by their own superstars in publicized cases. ORI should never have turned it over to Pitt."

If the filing of Fisher's suit had any role in

THE CANCER LETTER

Editors: **Kirsten Boyd Goldberg**
Paul Goldberg
Founder & Contributing Editor: **Jerry D. Boyd**

P.O. Box 15189, Washington, D.C. 20003
Tel. (202) 543-7665 Fax: (202) 543-6879

Subscription $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.

precipitating the suspension of the inquiry panel's proceedings last week, it was not the only factor, sources said.

The other consideration was the scope of the investigation chosen by Pitt.

Pitt's Inquiry Departs From ORI Mandate

Originally, ORI asked Pitt to look into potential misconduct by Fisher and Redmond, stemming from continued use of data from St. Luc in NSABP publications, while not disclosing that the data was fraudulent.

However, Pitt added an assortment of other allegations: failure to monitor endometrial cancer caused by tamoxifen, failure to implement procedures for auditing and failure to disclose funding from pharmaceutical companies.

Further broadening the inquiry, Pitt lawyers expanded the inquiry to include allegations against Wickerham, the NSABP official responsible for the cooperative group's audits.

The Cancer Letter has obtained a copy of a letter outlining the scope of the investigation. An excerpted version of the letter appears on page 4.

As they examined the charges, panel members were instructed to use a definition of misconduct that was broader than the definition used by ORI. Under ORI's guidelines, misconduct is defined exclusively as fabrication, falsification, plagiarism or other practices that seriously deviate from those accepted in the scientific community.

Pitt's definition also includes failure to protect human subjects and failure to meet material legal requirements governing research.

Fisher: Torrent of Questions

In his suit, Fisher said that in the course of the inquiry he has never been formally notified about the allegations against him and has been overwhelmed with a torrent of questions.

"On June 10, Pitt delivered to Dr. Fisher a stack of documents approximately 15 inches thick, indicating that he was to respond to the inquiry panel to the information contained therein," the complaint states.

"On June 17, Pitt advised Dr. Fisher to respond to 19 pages of financial material.

"On June 24, Pitt advised Dr. Fisher to respond to the transcript of a six-hour June 15 Congressional Subcommittee hearing.

"This torrent of material, coupled with Pitt's vague and overbroad definition of 'misconduct' denies Dr. Fisher due process and a reasonable opportunity to defend himself because it provides Dr. Fisher with no real notice of the charges against him or reasonable time to respond...

"To date... allegations against Dr. Fisher have not been adequately specified. Further, the charges are being shaped and brought by plaintiff's former counsel, defendant Michaelson," the suit stated.

The suit seeks Fisher's reinstatement as chairman of NSABP, the removal of Michaelson and his firm from representing the university in matters involving Fisher, and a halt to Pitt's "financial and other interests in obtaining from the inquiry panel it convened an adverse determination against Dr. Fisher."

A New Strategy for Fisher

Soon after his lawyers filed the suit, Fisher consented to face Pittsburgh reporters in a news conference.

"After being and doing what I did for so many years, and then suddenly one day to be called and told that I was no longer going to be the chairman of this thing, and there was no due process or anything else, that was a devastating thing for me," Fisher said.

"I've been unwilling to talk about it at all to anybody, and didn't for a long time," he said, according to a story in the July 13 Pittsburgh Post-Gazette.

"It was with extreme reluctance and dismay that I decided to take the Univ. of Pittsburgh to court," Fisher said to reporters. "As you know, I've been associated with the university for the past 35 years, and it was no easy matter to realize that I had been summarily dismissed from my position.

"This illegal action came despite the fact that my work has produced over the years many millions of dollars in research grants and great prestige to the university," Fisher said.

Opening himself to an hour of questions from reporters is a new strategy for Fisher, particularly since the start of the controversy. In recent months, even when he discussed NSABP at scientific meetings, Fisher took no questions.

"That was the strategy prepared for him by the university," said David Kosick, vice president of the St. George Group, a Pittsburgh-based public relations firm that represents Fisher.

Scope Of Panel's Inquiry Outlined In Confidential Letter

The following is the excerpted text of a confidential letter outlining instructions for the three-member panel conducting an inquiry into possible scientific misconduct by three officials of National Surgical Adjuvant Breast & Bowel Project. The document, dated June 7, was signed by George Bernier, dean of the Univ. of Pittsburgh School of Medicine and Donald Matison, dean of the Graduate School of Public Health.

The scope of the panel's inquiry is ultimately a question for the panel's own determination, depending upon what issues arise during the course of the inquiry... As a starting point... we have identified... four matters into which we believe the panel should inquire, as the panel addresses whether a formal investigation is indicated:

(1) Did one or more of the respondents know data from St. Luc Hospital were falsified or fabricated, yet include those data in NSABP publications? If so, was the inclusion improper?

(2) Did one or more of the respondents fail to collect, analyze or report in a timely manner adverse effects of tamoxifen, particularly an increased risk of endometrial cancer? More specifically, did one or more of the respondents:

(a) fail adequately to monitor the effects of tamoxifen in causing EC as those effects manifested themselves in the NSABP trials;

(b) fail adequately to disclose the known risks of EC to subjects in consent forms and in subsequent notifications in the course of the NSABP trials; or

(c) fail to fulfill their disclosure, reporting and compliance obligations to the university's institutional review board, the drug manufacturer ICI/Zeneca, NCI, the Office for Protection from Research Risks, FDA, the scientific community or the research subjects, concerning adverse effects of tamoxifen in causing EC in NSABP trials? If so, was the failure improper?

(3) Did one or more of the respondents fail to design or implement NSABP procedures for auditing the practices that would ensure the integrity of the data on which NSABP's scientific conclusions were based? More specifically, did one or more of the respondents allow the NSABP to:

(a) fail to perform sufficiently frequent, comprehensive and competent audits to detect significant irregularities or errors in the data;

(b) fail promptly and reliably to follow up on remedial action to ensure that the irregularities or errors were corrected and not continued? If so, was allowing that failure improper?

(4) Did one or more of the respondents accept, or fail to disclose, funding for their research or other activities provided by drug manufacturers (including, but not limited to, ICI/Zeneca)? More specifically, did one or more of the respondents:

(a) permit unjustifiable conflicts of interest by accepting research funding, consulting fees, honoraria, reimbursement of expenses or other benefits from drug manufacturers that stood to gain from respondents' research, or

(b) fail adequately to disclose such benefits to the university, NCI, scientific journals or other entities? If so, was one or more of the respondents' inaction or action improper?

Conflict Of Interest

PHS Proposed Rule Places Bias Review On Institutions

Institutions that apply for research funding from the Public Health Service will be required to review for potential bias the financial interests of investigators, according to a proposed rule.

Under the proposed rule, investigators are required to disclose to the institution "a listing of significant financial interests." Institutions are to review the disclosures and "determine the acceptability of the reported financial interests and act to protect PHS-funded research from any bias that is reasonably expected to arise from those interests."

The proposed rule, titled "Objectivity in Research," was published in the June 28 Federal Register. It was formulated following the publication by NIH of proposed conflict of interest guidelines in 1989 (**The Cancer Letter**, Nov. 10, 1989).

Awardee Institution's Responsibility

Under the proposal, institutions are required to "assume responsibility for ensuring that the financial interests of the employees of the institution do not compromise the objectivity with which such research is designated, conducted or reported."

According to PHS, "many respondents to earlier proposals stated that the primary responsibility for

setting guidelines and maintaining compliance should rest with each awardee institution." The proposed rule sets performance standards and charges the institutions with development of compliance procedures, PHS said.

All PHS-funded research is covered except phase I projects under the Small Business Innovation Research Program.

$5,000 Or 5 Percent

The proposed rule defines "significant financial interests" as "any interest of monetary value exceeding a defined threshold of value ($5,000) or percentage of ownership (5 percent or more) that would reasonably appear to be directly and significantly affected by the research funded by PHS or proposed for funding. It does not include interests in SBIR applicant institutions, income from seminars sponsored by public or nonprofit entities, or income from service on advisory committees or review panels for public or nonprofit entities.

Interests of the investigator's spouse and dependent children are included.

PHS said it was specifically requesting comment on whether this minimum threshold for disclosure is appropriate to ensure that research is not biased by the financial interests of the investigators. PHS also is seeking comment on whether provisions of the rule might "inadvertently hamper socially desirable research."

Costs to implement the proposed rule will not reach $1,000 in staff time per institution, or $1 million a year across all institutions, the PHS said.

Comments on the proposed rule are being accepted until Aug. 29. Comments may be addressed to: Dr. George Galasso, Associate Director for Extramural Affairs, NIH, Shannon Building, Room 152, 9000 Rockville Pike, Bethesda, MD 20892, Tel: 301/496-5356.

Extramural Program Next Target For Reinventing NIH

NIH, having reviewed its intramural research program last year, is turning its focus to the extramural grants program.

Last week, NIH Director Harold Varmus led a "roundtable" discussion with a group of extramural scientists on "reinventing" the NIH grant system.

Scientists seeking NIH grant support have complained in recent years about the review system that appears to "nitpick" research proposals. NIH officials and study section members have said that the increasing competition for research dollars has resulted in a greater attention to detail in grant review.

Since he took office, Varmus has talked about NIH as a laboratory to implement ideas for "reinventing government."

NIH has been circulating suggestions for improving the extramural program. Some of the suggestions discussed at the roundable included:

--Fixed-dollar grants in categories of $50,000, $100,000, and $200,000 in order to avoid tedious review of budget calculations.

--In certain cases, shifting the emphasis of review from the research proposed to the investigator's past work.

--"Triage," a process in which reviewers would at an early stage identify noncompetitive grant proposals and quickly send investigators notices informing them of the deficiencies of their proposals.

NIH is experimenting with triage in certain study sections, and plans to extend the process to more study sections, sources said.

--"Just in time" submission of detailed information to NIH, such as item-by-item budget projections, as the information is needed.

The House Subcommittee on Labor, HHS, Education Appropriations has asked NIH for a complete review of the extramural grant program.

The report should, "at a minimum" provide advice on the distribution of funds across the NIH grant mechanisms, on changes in the design of funding mechanisms, and on the need for new funding mechanisms, the subcommittee said in its report on the NIH FY95 appropriations.

NIH is to select a panel from outside the NIH community to conduct the review and submit a report by next February.

Study of Unfunded Researchers

In a preliminary report to the subcommittee, NIH tracked the career paths and funding for researchers who unsuccessfully applied for NIH grants in FY90.

According to the study, 39 percent of the unsuccessful applicants remained unfunded at the end of 1993. However, of those applicants who scored in the top 50 percent, only 10 percent remained unfunded.

Varmus, in a letter to the subcommittee, supported

an expanded study of unfunded researchers.

The study tracked 14,726 investigators who applied for the traditional NIH research project grant (R01) and First Independent Research Support and Transition (R29) grants.

Of those, 3,777 received an R01 or R29 in FY90. Another 2,605 researchers received funding in FY90 under other grant mechanisms, and 8,344 remained unfunded. Between FY91 and FY93, 2,496 of the unfunded researchers received NIH funding, leaving 5,848 researchers unfunded by the end of FY93.

The study compared those applicants who scored in the top half versus the bottom half of the group--a score better than the 50th percentile, or a priority score better than 250. Only 10 percent in the top half remain unfunded by the end of FY93, compared to 29 percent of the bottom half.

◆ ◆ ◆

A report by the National Research Council last month called on NIH to fund more training awards to meet the future needs for researchers in the biomedical and behavioral sciences.

NIH should fund an additional 1,100 National Research Service Awards by 1996, according to the report. The report also recommends increasing stipends to attract more young scientists into training.

NRSA slots should rise from the FY93 level of 15,211 to 16,260 by FY96, the report said.

In Brief

Glassman Moves To Anderson; Skin Disease Centers Awarded

(Continued from page 1)

ARMAND GLASSMAN has been named head of the Div. of Laboratory Medicine at M.D. Anderson Cancer Center. Glassman is the former director of clinical laboratories at Vanderbilt Univ. Medical Center. He succeeds Jose Trujillo, who died last year. . . . **THREE NEW** Skin Disease Research Core Centers have been funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and one center has been renewed, bringing the total number of centers to six. The four newly funded centers and their PIs are: Emory Univ., **S. Wright Caughman**; Brigham & Women's Hospital, **Thomas Kupper**; Vanderbilt Univ., **George Stricklin**; and Case Western Reserve Univ., **Craig Elmets**. The two additional centers are at Yale Univ. and Univ. of Texas Southwestern Medical Center. **Julia Freeman** directs the centers program at NIAMS. . . . **MARVIN ROTMAN**, SUNY Health Science Center, became president of the American Radium Society at the society's meeting this spring. **Robert Byers**, M.D. Anderson Cancer Center, is president-elect; **Thomas Griffin**, Univ. of Washington Medical Society, is secretary, and **H. Rodney Withers**, UCLA Jonsson Comprehensive Cancer Center, is treasurer.

RFAs Available

RFA CA-94-026

Title: **Prevention Clinical Trials Utilizing Intermediate Endpoints And Their Modulation By Chemopreventive Agents**

Letter of Intent Receipt Date: Aug. 25

Application Receipt Date: Oct. 13

The NCI Div. of Cancer Prevention and Control invites applications for cooperative agreements to support clinical trials that are directed toward examining the role of various chemopreventive agents and/or diet in the prevention of cancer. This is a follow-up to earlier RFAs that had requested grants, and then later, cooperative agreement applications in this area.

Applications may be submitted by domestic and foreign for-profit and non-profit organizations. The NIH cooperative agreement mechanism (U01). The recipients will have primary responsibility for the development and performance of the activity. However, there will be government involvement with regard to 1) assistance securing an Investigational New Drug approval from FDA, 2) monitoring of safety and toxicity, 3) coordination and assistance in obtaining the chemopreventive agent, and 4) quality assurance with regard to the clinical chemistry aspects of the study. This RFA will be issued annually for two years. Approximately $1.5 million in total costs for the first year will be committed. Project period cannot exceed five years. Three to five awards are anticipated.

The major objective of this solicitation is to encourage cancer chemoprevention clinical trials that utilize biochemical and/or biological markers to identify populations at risk and/or to provide intermediate endpoints that may predict later reduction in cancer incidence rates. These studies may be developed in phases, including a pilot phase, which could later proceed to a full-scale intervention. The main emphasis should be on small, efficient intervention studies aimed at improving future research designs of chemoprevention trials, providing further biologic understanding of the trial results, or providing better, more quantitative and more efficient endpoints for these trials. After successful completion of the pilot phase (i.e., demonstrated

modulation of marker endpoints by the intervention), subsequent studies could include a definitive clinical trial monitoring the test system, a cancer incidence or mortality endpoint, and a designated agent.

Investigators may apply at this time for the pilot phase, or submit an application for both the pilot and definitive trial studies. However, if the application is for the pilot phase only, it must include a description of its relevance to a broad clinical application, including the chemopreventive agent, marker test system, and study population which could later be the subject of a full-scale, double-blind, randomized, risk reduction clinical trial. Intermediate marker trials of breast cancer chemoprevention are especially encouraged.

Inquiries: Marjorie Perloff, Div. of Cancer Prevention and Control, NCI, Executive Plaza North, Suite 218, Bethesda, MD 20892-4200, Tel: 301/496-4664, FAX: 301/402-0553.

RFA CA-94-022

Title: **Research Program Grants In Chemoprevention**

Letter of Intent Receipt Date: Sept. 1

Application Receipt Date: Oct. 20

The NCI Div. of Cancer Prevention and Control invites cooperative agreements to support a research and development program of multiple projects directed towards chemoprevention of cancer, requiring a broadly based and multidisciplinary approach. Applications may be submitted by domestic and foreign for-profit and non-profit organizations. This RFA will use the cooperative agreement (U19) mechanism. If it is determined that there is a sufficient continuing need, NCI will invite recipients of awards made in FY 95 under this RFA to submit competitive continuing applications.

Recipients will have primary responsibility for the development and performance of the activity. However, there will be government involvement with regard to 1) assistance in securing an Investigational New Drug approval from FDA, 2) coordination and assistance in obtaining the chemopreventive agent, 3) monitoring of safety and toxicity and, 4) quality assurance of the clinical chemistry aspects of the study. Awards will not be made until all arrangements for obtaining the IND and the agent are completed. Final awards will consider not only the cost of the clinical trial but also the cost of the agent and, if necessary, its formulation.

Approximately $4 million in total costs for the first year for project periods up to five years will be committed. Four to six awards are anticipated. Earliest feasible start date will be July 1995.

To be eligible for awards, the application must include a minimum of three scientifically meritorious projects, one of which must involve a clinical trial. The theme might involve a particular agent or class of agents, populations, sites, or surrogate markers. Relevant preclinical and clinical ancillary projects might include in vitro and in vivo (animal) efficacy studies, pharmacokinetic and pharmacological evaluations, biomarker studies, and nested case control evaluations. The application should include a sufficient number of scientifically meritorious projects to promote an effective collaborative effort among the participating investigators.

This particular type of research project cooperative agreement (U19) builds on the leadership of a key principal investigator and the interaction of the participating investigators in order to integrate the individual projects in a way that accelerates the acquisition of knowledge beyond that expected from the same projects conducted separately, without combined leadership or a common theme. Individual investigators may apply their specialized research capabilities to basic, developmental, and clinical aspects, as they relate to the focused central theme of the overall project. This grant mechanism also offers a special way to achieve an economy of effort through the sharing of personnel, facilities, equipment, data, ideas and concepts.

The principal investigator of the research program cooperative agreement must be an established scientist with a strong record of accomplishment, who is substantially committed to, and capable of, exercising the responsibility for the scientific leadership, integration and administration of a major effort in cancer prevention. The component projects should be directed by investigators who are experienced in the conduct of independent research and whose backgrounds and interests relate sufficiently to one another in order to allow for integrated group pursuits.

Inquiries: Marjorie Perloff, Div. of Cancer Prevention and Control, NCI, Executive Plaza North, Suite 218, Bethesda, MD 20892-4200, Tel: 301/496-4664, FAX: 301/402-0553.

Program Announcements

PA-94-079

Title: **Dna Damage, Genomic Instability And Breast Cancer**

The NCI Div. of Cancer Etiology invites grant applications from interested investigators through a Program Announcement to establish whether or not there is greater genomic instability associated with individuals in families with hereditary breast cancer than in individuals that do not have a family history of cancer. This initiative is in response to Congressional language that NCI emphasize studies on the etiology of female breast cancer as one of its top priorities. Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private. This PA will be supported through the NIH research project grant (R01). Because the nature and scope of the research may

vary, it is anticipated that the size of an award will vary also.

The goal of this PA is to encourage research on human breast cancer using molecular, biochemical and cytogenetic techniques to determine whether or not a genomic instability in non-tumorigenic cells is associated with familial breast cancer family members both with and without cancer. Normal individuals with no family history of cancer could serve as controls. Suitable cells for this approach might include circulating lymphocytes, normal breast epithelial cells, normal fibroblasts or other appropriate cell types. The term "genomic instability" is taken broadly to mean a significant difference, presumably a decrease from an established normal base line, in any of various parameters expected to decrease the integrity of the cellular genome or its expression.

Study of parameters toward this end could include, but need not be limited to: 1) Determination of the relative capacity of suitable cells from members of breast cancer families to repair DNA damaged by either radiation or chemical carcinogens. Analogous cells from individuals who do not have a family history of cancer would serve as normal controls. 2) Determination of the relative abilities of suitable cells from breast cancer family members to deactivate genotoxic chemicals compared with those from normal controls. 3) Determination of the relative capacity of suitable cells from breast cancer family members to repair chromosome or chromatid damage from radiation or chemicals compared to those from normal controls. 4) Comparison of the sensitivity of appropriate cells from breast cancer family members and those from normal controls to the initial damage of DNA by radiation or chemicals. 5) Comparison of the relative capacities of suitable cells from breast cancer family members and those from normal controls to maintain the primary sequence of DNA, i.e., replication fidelity, proof reading capacity, prevention of DNA damage and recombination fidelity.

Because these investigations can involve several disciplines, both interdisciplinary studies and more focused investigations are appropriate.

Inquiries: Raymond Gantt, Div. of Cancer Etiology, NCI, Executive Plaza North, Suite 530, Bethesda, MD 20892, Tel: 301/496-9326, FAX: 301/496-1224.

PA-94-080

Title: **Genetic And Phenotypic Markers For Ionizing Radiation-Induced Breast Cancer In Rodent and Human Cells**

The NCI Div. of Cancer Etiology invites grant applications from interested investigators through a

Program Announcement to study changes of gene expression that are induced by exposure of pluripotent, or partially transformed, rodent and human mammary epithelial cells to ionizing radiations; and to define the role of such gene sequences in the progression to radiogenic breast cancer in rodent models. This initiative is in response to Congressional language that NCI emphasize studies on the etiology of female breast cancer as one of its top priorities. Applications may be submitted by domestic and foreign for-profit and non-profit institutions, public and private.

This PA will be supported through the NIH research project grant (R01). Because the nature and scope of the research proposed in response to this PA may vary, it is anticipated that the size of an award will vary also.

Young adult women and adolescent females under 20 years of age may be unusually susceptible to ionizing radiation- induced breast cancer (e.g., atomic bomb survivors, young female Hodgkin's lymphoma patients treated by radiotherapy). This PA encourages research applications to study the etiologic and mechanistic basis for the apparent susceptibility of pluripotent cells implanted into the developing breast tissue of rodents to undergo malignant transformation by ionizing radiation. It will focus on the characterization and analyses of the genes and gene products that may be differentially expressed during the progression of these precursor, or partially transformed, rodent mammary epithelial cells into malignant breast cancers. Particular emphasis will be given to defining the possible etiologic roles of such gene sequences in the early stages of progression prior to malignancy (e.g., mutations that result in increased dysplasia and loss of differentiation capabilities in vivo; acquisition of growth factor and hormonal independence for cellular proliferation in vitro). Where feasible, comparative in vitro or in vitro/in vivo studies of the effects of ionizing radiation on non-malignant human mammary epithelial cells will be encouraged. Because of the scope of the studies, involving both whole animals and molecular and cellular endpoints, multidisciplinary applications are encouraged.

The PA includes, but is not limited to:

—A determination of the susceptibility and involvement of precursor-like mammary epithelial cells in radiation-induced breast cancer in the developing mammary tissue of young female rodents;

—The isolation and subsequent genetic and biochemical analyses of gene sequences and gene products that are differentially over- or under-expressed during progression to radiogenic breast cancer in rodent and, if feasible, in human breast epithelial cells;

—The assessment, following radiation exposure, of differentially expressed genes, proteins or mutations in breast epithelial precursor cells to serve as biomarkers of preneoplastic lesions for radiation-induced breast carcinomas in rodents and humans.

Inquiries: Richard Pelroy, Div. of Cancer Etiology, NCI, Executive Plaza North, Room 530, 6130 Executive Blvd., Bethesda, MD 20892, Tel: 301/496-9326, FAX: 301/496-1224.