THE CANCER LETTER

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Centers Agree To Broader Phase 1 Availability; Cool To Idea Of Distributing Group C Drugs

The Cancer Therapy Evaluation Program of NCI's Div. of Cancer Treatment plans to make significant changes in four of its areas of activity with the intent to increase participation of cancer centers in

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In Brief

Gerald Dodd, Walter Lawrence Head ACS; Reauthorization Bills Expected Early '91

GERALD DODD, M.D. Anderson Cancer Center, was elected president of the American Cancer Society at the society's annual meeting this week in Atlanta. **Walter Lawrence,** Medical College of Virginia, was elected vice president and president-elect. New medical officers of the ACS Board of Directors are **Irvin Fleming,** of Memphis, TN, and **Reginald Ho,** of Honolulu, HI. John Seffrin, board chairman, will complete his two year term, as will Stanley Shmishkiss. Law officers include Frank Fisher and Larry Fuller, and newly elected secretary, **Charles Osborn,** of Lima, OH. . . . **REAUTHORIZATION** update: Bills to renew the authority of NIH probably will be introduced early in the 102nd Congress, according to Congressional sources, and the House bill is expected to include a provision that would overturn the fetal tissue research ban. There is some discussion of a similar provision being inserted into the Senate bill. No changes are expected in the National Cancer Act. Meanwhile, the lack of authorization will pose no problem to NCI construction funding, NCI sources said, since money was appropriated in the FY 1991 budget. . . . **INTERNATIONAL COUNCIL** for Coordinating Cancer Research has negotiated funding of a $30,000 grant from the French Assn. for Cancer Research and the Komen Foundation for an international research project on breast cancer. The project, "Regulation of Estrogen Receptor in Human Breast Cancer," is lead by Pierre Chambon, Institut Chimie Biologique, Strasbourg, France, and Mary-Beth Martin, Georgetown Univ. . . . **LUTHER BRADY** of Hahnemann Univ. has received an honorary degree, Doctor of Science Honoris Causa, from Lehigh Univ., for outstanding contributions in oncology. Brady, with Ned Heindel, developed a research program in radiation sensitizers and monoclonal antibodies. . . . **ALLAN OSEROFF** has been appointed head of the dermatology department at Roswell Park Cancer Institute and professor of dermatology at the State Univ. of New York (Buffalo) School of Medicine & Biomedical Sciences. He was staff dermatologist at New England Medical Center.

Centers Agree To Broader Phase 1, Other CTEP Plans; Cool To Group C

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those activities. CTEP Director Michael Friedman and Investigational Drug Branch Chief Michael Hawkins discussed those changes last week with center directors and their representatives at a meeting in Bethesda.

The changes include:

* Broadening the availability of phase 1 drugs to include cancer centers which are not members of NCI's contract supported Phase 1 Working Group.

* Relaxing CTEP's approval criteria for proposed developmental and pilot studies, relying more on peer review (for trials proposed in a funded RO1 or PO1 grant) or institutional controls.

* Permiting a limited number of centers to distribute directly Group C drugs to physicians in their regions, a task heretofore handled exclusively by CTEP.

* Developing a "treatment referral service" through which CTEP would channel the calls it receives ("Two or three a day," Friedman said) for treatment advice to participating centers. Initially, the service will be limited to requests involving breast and ovarian cancer.

Friedman had sent a letter to cancer center directors last spring asking for suggestions on how CTEP and centers could develop collaboration and improve on their interactions. In the responses, "there were three main issues that seem to be of concern," Friedman said. These were "increasing access to phase 1 agents; increasing the role of cancer centers in the distribution of Group C agents; and a feeling that CTEP sometimes appears too restrictive."

CTEP's presentation of its proposals for meeting those concerns follows:

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Availability of phase 1 agents

During the period of 1976-1990, NCI phase 1 trials were limited to NCI's Phase 1 Working group which consisted of phase 1 contractors as well as investigators with specific expertise or experience with the particular drug to be tested. While this policy has never formally been changed, over the years fewer and fewer phase 1 studies have been done by noncontractors. Currently, there are an unprecedented number of noncontract institutions that are highly qualified to conduct these early trials. In addition to providing the data typically collected on phase 1 trials, many of these institutions have established laboratory research interests which could be integrated into the conduct of the clinical trial.

We are sympathetic to the argument that NCI should make phase 1 agents available for study at such institutions.

Nevertheless, duplication of trials should be avoided or minimized. Even assuming that drug supply is adequate (which is often not true in the early development of a drug), we feel that duplicative trials should be avoided for the following reasons:

1. In phase 1 the number of patients being treated with subtherapeutic doses of an agent should be minimized.

2. The initial phase 1 studies should be based on the optimal schedules identified in preclinical pharmacology and toxicology studies.

3. In phase 2 the number of patients being treated with an ineffective dose and schedule should be minimized.

4. Duplicative trials provide no new knowledge and hence waste resources (even if direct NCI money is not involved).

In light of the above, we propose the following for the conduct of phase 1 trials:

A. As the IND is being prepared, CTEP would notify our phase 1 contractors and other institutions with peer reviewed expertise in the conduct of early clinical trials that we will be soliciting phase 1 trials. The number of these trials may be limited by drug supply or the development plan of the pharmaceutical sponsor.

B. Letters of intent would be submitted by interested investigators outlining the proposed trial, indicating the clinical, pharmacokinetic, and biological studies which would be conducted as well as an anticipated accrual rate and initiation and completion times of study. All phase 1 and many pilot studies should have laboratory correlative studies.

C. Based upon laboratory and clinical strengths, the proposals of greatest scientific merit and drug

development impact would be selected by CTEP staff.

D. Studies would be monitored by NCI's Clinical Trials Monitoring Service (CTMS, currently Theradex). Data would be presented at the phase 1 meeting and would be used to make decisions regarding subsequent development of the agent.

Centers representatives at the meeting generally were supportive of the proposal, and also of Friedman's suggestion that information exchange among those doing phase 1 studies might be enhanced by an "electronic bulletin board" which CTEP may establish. This would provide regularly updated information on ongoing phase 1 and pilot studies.

CTEP's role in evaluating the rationale for the conduct of a study.

One of the areas of greatest controversy is CTEP's evaluation of the strength of the rationale for the conduct of a study, usually phase 1 or pilot studies involving the combination of agents. Frequently, this dialogue between CTEP and the investigator is productive; but not always.

The argument has been made that if a rationale satisfies the investigator (he or she believes that there is not a clearly superior idea to be tested) the study should be approved. Since frequently the investigator is interested in doing only his or her proposal, the disapproval of the proposal does in fact waste patient resources since no alternative trial is implemented. While the number of proposals that actually have been turned down has been very small, there may be considerable, and sometimes nonproductive debate before CTEP and the investigator agree on the study to proceed.

The proposal: Developmental and pilot studies must still conform to accepted clinical trials methodology in all respects (including adequate accrual rate and appropriate patient population). For a clinical trial specifically proposed in a funded RO1 or PO1 CTEP will endeavor to supply a necessary investigational agent (if available). An adequate protocol document which fulfills all regulatory requirements is always necessary.

In the absence of a funded RO1 or PO1, as long as the protocol is methodologically sound and if there is adequate assurance of patient safety, CTEP will **not** disapprove a proposal based upon what we feel is an incompletely convincing scientific rationale. CTEP will convey its concerns, and offer suggestions and advice, but in the absence of a clearly superior competing idea will be more flexible in study approval.

No one objected to the proposal.

Distribution of Group C agents

There are three principal objectives of the current Group C mechanism:

1. Wide availability of agents known to be effective in specific malignancies (i.e., therapeutic use of investigational agents). [Ed. note: by definition, these are drugs which have not been approved by FDA for marketing].

2. Collection of additional data for scientific and/or FDA registrational purposes.

3. Engaging more physicians in cancer clinical trials.

The highest of these priorities to NCI is the greater availability of effective therapies to patients. In the system that is currently being used, physicians contact NCI directly to obtain Group C drugs.

New investigators are registered (i.e., complete a form 1572), it has been confirmed that the patient has the disease for which the agent has been given Group C status, and the drug is shipped directly to the physician. Data, if being collected, are submitted on forms provided at the time of patient registration.

Proposal: In an attempt to increase the use of Group C drugs, NCI is prepared to implement, on a two year trial basis, a limited program in which one or two cancer centers would directly distribute Group C drugs. These centers will be allowed to cross file on the NCI IND and assume the responsibilities of a drug sponsor. The cancer center would thus be responsible for registering investigators, assuring that only patients who meet the Group C guidelines are treated, maintaining drug accountability records, and reporting to FDA. Copies of reports sent by the center to FDA also will be sent to NCI. The drug will be sent to the cancer center either by NCI or the drug company.

For those agents on which data are being collected by NCI, a decision will be made regarding the need to include data from patients treated under the center's IND. Naturally, at the same time, the current system for centralized distribution of Group C agents by NCI will continue.

As it turned out, only one center, the Univ. of Arizona Comprehensive Cancer Center, has expressed interest in handling Group C distribution. Director Sydney Salmon sees it as an opportunity to better serve the region, develop more allegiance to the center, and to increase patient accrual to clinical trials.

Other centers were not very interested. "You would be out of your mind to take this on," one center director commented.

They were even more cool when Friedman said that no funds would be available to help defray the

administrative costs of distributing the drugs.

The drugs themselves will continue to be supplied free by NCI or by pharmaceutical companies.

Center representatives at the meeting agreed that CTEP's handling of Group C distribution has worked out well and suggested that it be continued. Friedman said CTEP would proceed with bringing the Arizona center into the process, and offered to do so with one additional center, but no one at the meeting volunteered to join in.

"If this catches on and all centers join in the distribution, it would still be difficult to shut down completely here," Hawkins said.

"Some physicians will find it easier to just go directly to NCI," David Goldman, director of the Medical College of Virginia Cancer Center, commented.

Treatment referral service

Friedman said that this proposal will only "formalize something that already exists." He was referring to the calls NCI receives from physicians in which they say, "I've got a patient who has failed [initial or secondary treatment], so what do I do next?" CTEP responds in a variety of ways, depending on the type and stage of cancer, location of the patient, suitability for clinical trial entry, etc.

"We want to make cancer centers an integral part of this," Friedman said.

"It is our perception that there is an increasing interest in using investigational drugs by community physicians who are not participating in clinical trials," Hawkins said.

CTEP proposes to refer calls, initially only for breast cancer and ovarian cancer patients, to clinical studies, usually phase 3 cooperative group trials, or to cancer centers, generally for evaluation and treatment. Referrals would be to centers and cooperative group physicians close to patients' homes, if possible.

Hawkins said his would increase availability of investigational agents to patients, and increase accrual to clinical trials.

Friedman said that participation by groups and centers would be voluntary.

"We see this as a way of capturing data that otherwise might be lost, and as a way to help cancer patients," he said.

Although center representatives at the meeting had some questions about how decisions would be made on where to refer [answer: generally to the closest center, or in the case of multiple centers in an area, all would be mentioned; availability of protocols at a given center suitable for the patient being referred], they did not object to the proposal.

DCBDC Board Approves Concepts For Four Education Initiatives

The Board of Scientific Counselors of the Div. of Cancer Biology, Diagnosis, & Centers has given concept approval to four initiatives which will support about $5.5 million a year in cancer education and training grants.

The concepts were for a program announcement soliciting applications for preventive oncology academic awards to MDs and PhDs; and RFAs for collaborative education programs in cancer prevention and control; cancer education programs in pain management, rehabilitation, and psychosocial issues; and cancer center community outreach education programs, which would be limited to NCI designated cancer centers.

Concept statements and board discussion:

Preventive oncology academic awards (KO7). An anticipated 15 awards will be made at a direct cost of approximately $70,000 per award per year, plus indirect costs not to exceed eight percent. The total cost will be approximately $1.13 million per year. This program announcement will use the existing K07 grant mechanism, with nonrenewable project periods of three to five years depending on the applicant's background, needs, and objectives.

NCI proposes to invite applications from individuals who hold a PhD or MD, or equivalent professional degrees for career development awards in cancer prevention. These awards would provide support to individuals for research and training in schools of medicine, osteopathy, public health, and cancer centers. Subject areas appropriate for awards under this program announcement include cancer relevant aspects of human genetics, human nutrition, behavioral and social sciences, biochemical and genetic epidemiology, prevention clinical trials, health education and promotion, nursing, and public health as they apply to cancer prevention and control research.

The scope of research projects to be used for the candidates' career training extend from the development and testing of hypotheses concerning cancer prevention, through design and implementation of interventions in defined populations, to large scale demonstration projects.

Candidates should have at least two years of postdoctoral research experience but not yet be fully independent investigators. Major target groups are professionals already proficient in clinical oncology, general epidemiology, psychology, behavioral sciences or other pertinent sciences who wish to make the transition to cancer prevention and control research and others who already have some training in cancer prevention and control but need to gain additional professional experience which will permit them to become fully independent investigators. This award also provides an optional opportunity to trainees who wish to participate in prevention and control research projects at NCI for three months or more.

The success of efforts to reduce cancer mortality and morbidity will depend in large part on the availability of a cadre of research scientists, clinicians, and educators who are capable of undertaking independent research related to the development and implementa-tion of improved interventions in areas of cancer prevention and control. Although several training mechanisms are

available for training in these areas, a very low percentage (less than 4%) of the major training grant mechanisms are in areas that are somewhat related to cancer prevention and control. Only two K07 applications were submitted to NCI in FY 90.

This low level of support demonstrates the need for an increased effort to train professional health personnel in research techniques necessary for the development and implementation of interventions that are designed to prevent cancer and to improve the early detection and diagnosis of cancer. The personnel trained under this career program are expected to have a significant impact in cancer prevention and control research efforts, particularly in projects designed to increase participation in programs that should result in earlier detection and diagnosis of cancer, particularly in special populations with increased cancer risk (i.e., ethnic groups, minority groups, and groups with low socioeconomic status); and to prevent cancer by the modification of behaviors and life styles related to increased cancer risk (i.e., tobacco use, altered diet). Thus, this award is to train individuals in areas of cancer prevention and control research that define high risk groups and test new methods of intervention that will reduce incidence and mortality in these groups.

The K07 grants provide salaries of up to $40,000 per year plus fringe benefits, provided the requested salary is consistent with the established salary structure of the grantee institution for persons of equivalent qualifications, experience, and rank. This salary may be supplemented by the grantee institution as provided by PHS policy. An additional allowance of up to $20,000 is included to cover the cost of tuition and fees, supplies, equipment, travel, salary for a research assistant, and other expenses necessary for the awardee's research and education program.

Vincent Cairoli, chief of the Cancer Training Branch, said that trainees in the K08 program now receive up to $50,000 in salary and that consideration is being given to permitting the same level for K07 recipients.

Although this is an ongoing program, Cairoli said that the number of applications has been dwindling. Five applications were submitted in 1988, with three being funded; four submitted in 1989, with two funded; and two were submitted this year, and both were funded. The program announcement is intended to stimulate more submissions, he said.

There are 13 with preventive oncology awards scattered around the U.S., Cairoli said. "The K07 people feel isolated. They want to establish networking. We hope we can get the present KO7 trainees and graduates of the program together at ASPO [American Society of Preventive Oncology, which meets annually in March]."

"In a sense, this is an affirmative action program," Board member Albert Owens said. "I'm supportive of it." So was the rest of the board, which approved it unanimously.

Collaborative education programs in cancer prevention and control. This will be a one time solicitation under the R25 cancer education grant mechanism. These awards will support predoctoral and/or postdoctoral positions; each award should not exceed a total of six training positions. Three postdoctoral positions will be the maximum number supported in any one year (see below the board's request to remove that limit, and staff's concurrence). Predoctoral salaries and fringe benefits of up to $12,000 and postdoctoral salaries and fringe benefits of up to $50,000 will be provided commensurate with the applicant institution's salary structure for persons of equivalent qualifications, experience, and rank. A cost of education allowance of up to $12,000 for tuition and other fees and a travel allowance of $800 will be provided for both predoctoral and postdoctoral students. Indirect costs for training grants cannot exceed eight percent of direct costs.

The maximum costs for grants supporting a full complement of six training positions would range from $162,000 (6 predocs x $27,000) to $285,000 (3 predocs x $27,000 + 3 postdocs x $68,000). Other combinations and fewer than six positions would cost less. A total cost of $2.5 million for the first year would support 10 or more renewable grants which will continue for five years.

The Cancer Training Branch proposes to invite grant applications that will support educational programs aimed at training new investigators in research skills useful in the design and implementation of cancer prevention and/or control intervention research. A major goal of this RFA is to develop a cadre of public health trained clinical oncologists. Other health professionals already schooled in areas of public health and the behavioral and social sciences could also be provided with basic knowledge in cancer biology and clinical cancer prevention trials and oriented toward careers in cancer prevention and control interventions. These complex cross disciplinary educational programs are likely to involve active collaborations among several institutions and departments such as those with cancer center support grants (P30), schools of public health, departments of community and preventive medicine, and other departments and institutions that have the necessary expertise and resources. Any of these entities may act as the applicant organization.

It is expected that these educational programs combining core curricula with ongoing cancer prevention research projects will provide students and health professionals with training ranging from research on interventions and their impact on defined populations to the broad, systematic application of the research results. There should also be an emphasis on providing the specialized skills needed for interventions in the underserved, elderly and minority populations that have an elevated incidence of cancer.

Major goals of this initiative are to increase the number of independent researchers in cancer prevention and to increase the number of clinical oncologists proficient in the use of public health approaches and behavioral techniques for the development and implementation of interventions designed to prevent cancer and to increase the early detection and diagnosis of cancer. A sufficient number of trained practitioners carrying out such interventions on a national scale could make a significant contribution to the reduction of cancer incidence and mortality.

There is a serious shortage of well qualified individuals prepared to conduct cancer prevention and control research. The situation is equally dismal for clinical oncologists who are proficient with public health principles and prevention techniques. Several studies analyzing the number of research grants and training trains in areas dealing with cancer prevention and control have uniformly demonstrated a very low percentage of grants in these important areas. For example, only one percent of the 1,460 trainees supported by the National Research Service Award program and less than four percent of the 1,600 trainees supported by major NCI training grant mechanisms are being trained in cancer prevention and control. Moreover, very few academic institutions have coordinated a curriculum and other essential elements relevant to preparing individuals for a career

in cancer prevention and control research and teaching.

Legislation for the National Cancer Act under "Cancer Control Programs" specifically states that the director shall establish programs that include "the demonstration of and the education of students of the health professions and health professionals in effective methods for the prevention and early detection of cancer and the identification of individuals with a high risk of developing cancer." This mandate has been amplified by the recent congressional appropriations hearings calling for greater NCI efforts in prevention and control.

All of these factors demonstrate the need for an initiative to increase the infrastructure of prevention investigators and to train professional health personnel who will be needed to play a major role in the development and implementation of cancer prevention and control intervention research projects. The personnel trained under this RFA are expected to make a significant impact on cancer morbidity and mortality by investigating new methodologies and interventions in defined populations; modifying behaviors and life styles related to increased cancer risk; and planning and participating in screening programs of high risk populations for earlier diagnosis of cancer.

A comprehensive program of this nature requires the integration of many diverse elements such as (1) a core curriculum covering topics in cancer biology and prevention, public health, and behavioral sciences; (2) cancer prevention and control research projects; (3) the availability of appropriate patient study populations and data bases; and (4) the availability of appropriate laboratory and clinic facilities. Principal investigators and applicant organizations must demonstrate the ability to organize and administer an interdisciplinary program such as this which requires linkage to other academic and programmatic components of the parent and/or collaborating institutions.

This initiative would provide training in cancer prevention and control through course work, hands on interventive practice and research experience. Depending on the type of education program proposed, the award would support predoctoral students who already have an MPH or MS or equivalent degree including health profession students and clinical oncologists and other postdoctoral students for up to three years.

An active research base of peer reviewed cancer prevention and control research should be available for the training of candidates enrolled in this program. The requisite faculty and commitment of sufficient faculty time are critical factors that must be available for this educational program. In developing and implementing a curriculum for training cancer prevention specialists, the details will depend to a large extent on the goals of the overall program and the participants. Graduates of the program should have some knowledge of cancer biology, including models of carcinogenesis and short term intervention endpoints that would allow one to monitor the efficacy of various interventions. Students should understand the research methodologies of key prevention related disciplines such as epidemiology and the behavioral sciences, as well as theories of health education and prevention and control. Examples of other courses that might have relevance to particular programs include biostatistics, qualitative and quantitative methods in research design and analysis, cancer surveillance and data use, behavior modification, nutrition related to prevention, health policy, health promotion, political science, economics, and ethics.

Each student should complete a hands on intervention project and undertake a thesis problem related to cancer prevention or control commensurate with their academic standing and goals. Research graduates should be able to design and conduct research on the efficacy and effectiveness of interventions in populations, while practitioner graduates should be able to apply the results of research studies to populations.

Board members Margaret Kripke and Albert LoBuglio suggested that the number of postdoctoral trainees permitted for each award be left to peer review rather than impose a limit of three. Cairoli agreed, and the board approved the concept unanimously.

Cancer education programs in pain management, rehabilitation, and psychosocial issues. This will be a one time solicitation using the R25 cancer education grant mechanism. Total cost is expected to be about $800,000 for the first year. It is expected that 10 grants averaging approximately $80,000 each total cost will be awarded and that each grant will continue for three years. Indirect costs for training grants are limited to the lesser of actual or eight percent.

These grants will support training activities such as short courses and/or workshops for health professionals in pain management, rehabilitation, and psychosocial issues affecting cancer patients and their families. Intent of this concept is to support cancer education programs that will facilitate the dissemination and application of information regarding state of the art procedures for effective pain control in cancer patients, for improving the rehabilitation of cancer patients and their reentry into the work place, and for using psychosocial knowledge and techniques to improve the well being of cancer patients.

There is a consensus among clinical oncologists, nurse oncologists, American Cancer Society, World Health Organization and a number of other lay organizations that there is inadequate control of cancer pain. One of the main reasons for failure is underdosing with narcotic analgesics. In addition to the reality of undertherapy, there are strong negative biases concerning drug addiction, legal requirements for narcotics, fear of failure, and the fear of quickening the patient's death. Although more pain research and analgesic drug development is needed, the proper application of current medications and techniques can relieve pain in most cancer patients.

At a recent workshop in Bethesda, it was stated that "as a general principle, every health professional involved in the treatment of patients with cancer should have demonstrated competence in the basic assessment and management of cancer pain." The group recommended that NCI use cancer education grants to stimulate cancer pain education programs at the undergraduate, graduate, and practice levels.

Progress has been made in many areas of psychosocial research including the ability to quantify many behavioral and subjective parameters. The use of psychosocial principles could have a significant impact on cancer by improving the psychosocial well being of cancer patients and their families, including pain management, and better acceptance of cancer patients by their peers, the work place, and the community after treatment.

This concept proposes to address this multidimensional problem by stimulating educational programs aimed at undergraduate and graduate health professionals, practicing physicians and nurses, and patients and their families. Cancer centers and other qualified organizations should establish interdisciplinary educational programs with expertise in oncology, nursing, psychology, sociology, and other disciplines. Short training courses, workshops, small discussion groups, and other innovative approaches can be used either locally or regionally to disseminate state of the art knowledge.

"This is a very critical area, but the budget for it is like spitting into a windstorm," Owens said.

LoBuglio, noting the interest in pain control expressed by Congress in the FY 91 appropriations legislation, said that "Congress needs to understand the problems involved. Reimbursement is difficult, and there is no staff in the community to do these things, other than salaried people in hospitals."

"Even where they do have (appropriate) people, they are not using the best techniques," Cairoli said.

The concept was approved unanimously.

Cancer center community outreach education programs. This will be a one time solicitation limited to NCI designated [core grant funded] cancer centers. Grants will be awarded for a three year period at annual levels not to exceed $100,000 plus eight percent maximum for indirect costs. NCI expects to make awards to 10 centers.

The grants will support multiple, continuing education programs for local and regional health care professionals, community leaders, and relevant community organizations. These education programs would provide state of the art information regarding the prevention, screening, diagnosis, and treatment of cancer.

These awards would provide support for the administrative and didactic costs associated with the continuing education sessions. The training sessions would include seminars, workshops, short courses and other appropriate formats which the applicant organization might propose. Arrangements should be made to provide CME credit for these courses.

Topics for these education programs should be selected on the basis of their relevance to the day to day activities of the community health care professionals and the benefit of the programs to underserved groups. The special problems and needs of ethnic, minority, and low socioeconomic populations should be addressed. Emphasis should be given to topics that would have the greatest impact on reducing cancer incidence and mortality and improving the quality of life for cancer patients in general.

There have been reports indicating that if the same state of the art prevention, detection, diagnosis, treatment, and care of cancer patients available at academic cancer centers were available at the local community level, there would be significant improvements in cancer incidence, morbidity, and mortality. Thus, there is a need to facilitate the transfer of this knowledge to the community health professionals who are responsible for caring for the majority of cancer patients and to community leaders and community organizations that have an educational responsibility to the public.

One of the essential programmatic elements of an NCI designated comprehensive cancer center is its role as a focal point for clinical and research training and for continuing education for health care professionals locally and within the region (e.g., how to use the PDQ system efficiently). This is to be accomplished in part by the provision of training in state of the art research and technology. The purpose of this RFA is to provide funding, on a competitive basis, for the development and implementation of this programmatic element at NCI designated comprehensive cancer centers and other NCI designated cancer centers that may be preparing for comprehensive status.

The resulting education programs are expected to have a significant impact on terms of cancer prevention, early diagnosis of cancer, and the quality of care of cancer patients. In addition, the programs should be of particular benefit to underserved communities and to groups with a disproportionate cancer incidence and death rates (e.g., minorities, people over age 65), since emphasis is to be given to topics that would be of special benefit to these target groups.

Board member Eugene Bauer asked why the grants would be limited to NCI funded cancer centers. "There are a lot of others out there."

Cairoli noted that these programs "are built in requirements for comprehensive centers, and if other centers want to achieve that status, this would help them get additional money for it."

"But if you limit to those centers, it would exclude many centers in areas where you would reach the population you want to reach," Bauer insisted.

"The facts are that we [comprehensive centers] are being asked to carry out these activities, but with no money from NCI," LoBuglio said. He is director of the Univ. of Alabama (Birmingham) Comprehensive Cancer Center.

"The issue is that comprehensive centers are regarded by Congress as doing pretty much this kind of activity, but without the money to support it," board member Ross McIntyre said. He is director of the Norris Cotton Comprehensive Cancer Center.

"What impact will a $100,000 award have on carrying out the mandate?" Kripke asked. "This is a Band-Aid."

"It would be helpful if centers knew they could get $100,000 and be assured that when they get their comprehensive status, it would not be taken away from them," McIntyre said.

"It's not a Band-Aid but a start," said Brian Kimes, director of DCBDC's Centers, Training, & Resources Program. "It's not unreasonable to limit now to NCI funded centers. If we expand it later to include others, okay. But we know that NCI centers have been reviewed, and have peer reviewed research."

Cairoli asked that the limit remain in the concept, and that the issue of expanding to other centers be considered when the first round of grants are up for renewal. The board agreed.

Recompetition Of Feral Mouse Breeding Colony Contract Approved

Recompetition of a contract for maintenance and housing of a feral mouse breeding colony received concept approval from the Div. of Cancer Biology, Diagnosis, & Centers Board of Scientific Counselors at its recent meeting.

The colony has been maintained through a contract with Hazleton Laboratories for the Oncogenetics Section of the Laboratory of Tumor Immunology & Biology. Robert Callahan, chief of the section,

presented the concept to the board. A summary of the concept statement follows:

Feral mouse breeding colony. Recompetition of a contract held by Hazleton Laboratories. Estimated annual total cost is $145,000, three year award.

This contract represents a major resource for the Oncogenetics Section and plays an integral role in the research of Drs. Robert Callahan, Gilbert Smith, Dan Gallahan, and Antonio Marchetti on the identification and characterization of mutations relevant to the etiology of mammary gland neoplasia. Their studies have focused primarily on three feral mouse strains which have unique characteristics that are pertinent to the study of mouse mammary tumorigenesis.

The current contract provides proper facilities and technical support for the housing, breeding, and maintenance of 1,000 feral and inbred mice. This includes technical help experienced in the handling and husbandry of feral mice, breeding feral mice, knowledge of requirements of outbred colonies, milking mice, observation of mice for early tumor development, surgery, dissection, injections, and preparation of tissues for histology.

The colony is composed of approximately 700 mice that are held long term (two years) for tumor development and 300 mice as a breeding nucleus. The breeding nucleus is composed of the three pedigreed outbred colonies of feral mice and the int-3/FVB transgenic mice. In addition, a limited breeding nucleus of the high incidence C3H/OuJ, as well as the low incidence BALB/c TT and FVB inbred mouse strains are maintained. Analysis of all tissue samples and specimens is performed by the Oncogenetics Section. Protocols for the injection of virus or virus infected cells, as well as for the breeding of new mouse sublines, is provided by the Oncogenetics Section.

These pedigreed breeding colonies represent a genetic and biological resource that is not commonly available. The research studies of the Oncogenetics Section depend on the mammary tumor tissue and normal tissues from these mice provided by the contract. The use of these feral mice has led to the identification of two new int loci that have not been previously described in mammary tumors of inbred mice.

At the present time there is no space on the NIH campus for housing a conventional mouse colony of this type, nor are there any plans to provide space for such an animal facility. Callahan investigated the possibility of combining this contract with existing DCBDC animal holding contracts and has determined that there would be no savings to the government.

Follow-Up Studies Of Thorotrast Win Concept Approval From DCE

The NCI Div. of Cancer Etiology Board of Scientific Counselors gave concept approval for a new contract for follow-up of persons exposed to the radioactive agent Thorotrast, used from the 1930s to 1950s for imaging.

Following is the concept statement for the proposed RFP, which the board approved unanimously:

Cancer following longterm exposure to radioactive Thorotrast. This is a concept for a new RFP. Proposed total funding $870,000, first year award $275,000; three years. There are few human populations available to study the carcinogenic effects of radionuclides ingested or injected into the body. One valuable source of data is provided by patients injected with Thorotrast (thorium dioxide), a radioactive radiographic contrast agent used between 1928 and 1954.

The objectives of this RFP concept are 1) to determine the risk of various malignancies in patients chronically exposed to internal alpha particle emitters, 2) to characterize the pattern of risk over time, 3) to refine dosimetry for increased precision in the determination of radiation risk estimates, 4) to apply vrious biochemical measures of radiation dose to learn whether a correlation exists between these measures of molecular damage and the estimated amount of Thorotrast exposure, and 5) to obtain lung tissue to characterize p53 and possibly other mutations.

It is estimated that over 3,000 Thorotrast exposed patients, previousy surveyed in the U.S., Sweden, Denmark and Portugal would be available for further study. Several of these earlier epidemiologic investigations also included control groups consisting of patients injected with nonradioactive contrast agents for similar indications as those injected with Thorotrast. A collaborative study of about 2,000 Thorotrast exposed patients and 1,200 nonexposed patients is anticipated. About 90% of these patients will have died. Only patients treated with Thorotrast in the course of cerebral angiography will be considered. Each population of patients would be re-identified and information collected on Thorotrast exposure, demographic variables, survival and disease occurrence. These populations would be followed forward in time and cause of death determined. For any populations without a nonexposed comparison group, population rates would be used to estimate expected numbers of cancers. Cumulative risks and patterns of risk over time would be evaluated.

Because multiple awards are envisioned, methods of study cannot be precisely described and will likely vary depending on the collaborators. For some countries, such as Sweden and Denmark, national cancer and mortality registries exist which can facilitate follow up. Other countries, such as the U.S. and Portugal, would have to apply more labor intensive techniques to trace patients. However, since each population has previously been identified and evaluated at least up to some period of time in the past, it is envisioned that only additional tracing and death certificate acquisition will be needed. Several of the known studies incorporated nonexposed comparison patients so that direct contrasts can be made. Other series will have to use national rates for comparison. Smoking histories for the lung cancer cases will be obtained to the extent possible, especially for subjects selected for biochemical evaluations. This information exists in the records of some of the series, but would have to be obtained from next of kin for others.

For subjects located alive, a proportion (perhaps 20 individuals) would be asked to donate blood for evaluation of biomarkers, such as GPA and chromosome painting. Somatic cell mutations will be measured using the GPA assay, which can be performed on a small sample of peripheral blood and will result in a measurement of the frequency of hemizygous or homozygous variant erythrocytes. Since the GPA assay requires heterozygosity for the MN blood group, it can be performed on only half the population (approx. 10 subjects). If the initial findings seem informative, the sample might be increased. For patients who developed lung cancer, tissue blocks would be requested and sent to the NCI Laboratory of Human Carcinogenesis for evaluation of the p53 gene. It is estimated that about 5-10 such blocks might be evaluated.

Main cost of the survey will be the re-identification and follow up of the populations. Cost estimates were based on three awards made. If fewer awards are made the cost would be less.