THE CANCER LETTER

Vol. 16 No. 45
Nov. 23, 1990

Price $195 Per Year US, Canada.
$220 Per Year Elsewhere

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

NCI Considers Seeking New Study Section For Clinical Research, Or Expansion Of E2

NCI has launched a movement aimed at improving access to resources for support of clinical oncology research, the key feature of which is either establishing a new NIH study section to review RO1 clinical oncology grants or expansion of an existing study section by adding more expertise in that area. The recommendation for a new or revamped study section came out of a workshop on training in clinical research in

(Continued to page 2)

In Brief

A Third Of Smokers Quit For Smokeout--Gallup; 77 Percent Pass Oncology Nursing Examination

ONE THIRD of all smokers participated in the American Cancer Society's Great American Smokeout in 1989, giving up cigarettes for a day, according to the Gallup Organization. About 5.3 million refrained from smoking on the day of the Smokeout, and an estimated 3.9 million did not smoke one to three days later. The goal for the 1990 Smokeout, held Nov. 15, was for at least one in five smokers to give up cigarettes for the day. . . . **2,638 NURSES** passed the Oncology Nursing Certification Corp.'s examination administered last September, or 77% of those who sat for the exam. Of those, 1,564 nurses passed for the first time and 461 renewed their credentials originally earned in 1986. There are now 8,772 oncology certified nurses. Next exam is scheduled for May 7. . . . **JANE PAULEY** narrates a 30-minute television program, "Once a Year...For a Lifetime," on the importance of mammography screening, aired on NBC stations Nov. 16 and Nov. 23 in various TV markets around the country. Check local listings. . . . **JOHN CHAPMAN**, a leading authority on radiobiology, has joined Fox Chase Cancer Center's division of medical science. Chapman directed the radiobiology program at Cross Cancer Institute in Edmonton, Alberta. He will direct the section of tumor biology and biophysics in Fox Chase's radiation oncology department. . . . **ROBERT MORETON**, vice president emeritus of M.D. Anderson Cancer Center, has received the 1990 Distinguished Alumni Award from Univ. of Tennessee College of Medicine, in recognition of "tremendous contributions" to the medical profession. . . . **JOB VACANCY:** European Organization for Research & Treatment of Cancer is seeking a director for its data center, in charge of 25 biostatisticians and data management personnel. Candidates should have experience in clinical trials, biostatistics or clinical experience and be willing to locate to Brussels, Belgium. Contact Chairman, Search Committee, EORTC Headquarters, 83 avenue Mounier-Bte 10, B-1200 Brussels.

NCI Considers New Study Section For Clinical Research, E2 Expansion

(Continued from page 2)
oncology held earlier this fall. The workshop was organized and conducted by the Centers, Training, & Centers Program of the Div. of Cancer Biology, Diagnosis, & Centers, as a continuation of a study by Emil Freireich.

Freireich, one of the premier, pioneer clinical oncologists in the development of cancer chemotherapy, has been working at NCI this year as special assistant to Director Samuel Broder. He is "on loan" from M.D. Anderson Cancer Center where he is director of the Adult Leukemia Service.

At Broder's request, Freireich has visited about 20 cancer centers and talked with 278 individuals including 102 trainees about major problems in training MDs in clinical oncology research and impediments to recruiting them into clinical cancer research. He has written a manuscript from that effort, "A Study of the Status of Clinical Cancer Research in the United States :(1990)", which will be submitted for publication in a professional journal.

Purpose of the workshop was to confirm that Freireich's manuscript was an accurate representation of the problems facing the clinical oncology research community, which it did; and to focus on how these problems are affecting the training of MDs who wish to pursue careers in clinical oncology research.

Workshop participants produced a report which included five major recommendations. These were presented to the boards of scientific counselors of DCBDC and the Div. of Cancer Treatment at their recent meetings. Response of the advisors, while generally supportive, was mixed.

THE CANCER LETTER

Editor: **Kirsten B. Goldberg**

Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

Subscription rate $195 per year North America, $220 elsewhere. ISSN 096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS Update.

Excerpts from the report, and BSC discussion follows:

A comprehensive approach to structuring programs for medical oncology research should set both short term and long term goals that will not only provide young physicians research training but also prepare them to compete successfully for research project grants (RO1, etc.) so that they can foresee the reasonable possibility of a successful career in clinical research.

The environmental resources available for training in clinical oncology research depend largely on the extent and type of funding available to clinical researchers, as well as on the various support mechanisms available for training young MDs wishing to pursue careers in research. The availability of peer reviewed research funds from NIH, in particular the training grants and the investigator initiated research program and project grants, is what provides academic recognition and success for clinical researchers, maintains high morale and purpose within the clinical research community, and sustains a culture that promotes high standards of experimental rigor within the field. It was the general feeling of the extramural clinical researchers who participated in this workshop that opportunities for peer reviewed support in clinical oncology were severely limited. Instead of spending a significant portion of their time and effort on peer reviewed research, senior clinical investigators are forced to do their research depending on funds from various tenuous sources (e.g. industry) in a piecemeal fashion and to spend the majority of their time in service activities. Thus, senior clinical investigators are placed at a considerable disadvantage compared to senior basic investigators in their ability to provide adequate environments for attracting, training, and retaining young MDs in clinical research.

A number of unique problems intrinsic to the clinical oncology research community were identified by the participants in the workshop. They concluded that these problems, if addressed, would enhance the environmental resources for training and would also increase the number of young MDs pursuing research careers in clinical investigations. The following areas were considered of importance:

1. Lack of access to the RO1 mechanism is the main problem faced by researchers wishing to pursue innovative clinical oncology research. Most clinical investigators do not submit RO1 grant applications because they fare very poorly in NIH study sections. There is no doubt that clinical research can be done

using the RO1 mechanism and that RO1s would be used, as they are for basic research, as an additional, significant, direct resource for training individuals at the graduate and postdoctoral levels. Clearly, the recent response of the research community to the DCT RO3 initiative (160 submissions with only 12 weeks notice) demonstrates the widespread interest of clinical researchers in obtaining investigator initiated, peer reviewed support. [The DCT RO3 initiative solicited applications for small grants to support clinical/laboratory correlative research].

It was the perception of a majority of the participants that the Experimental Therapeutics 2 (E2) Study Section in the NIH Div. of Research Grants, although consisting of highly qualified scientists and physicians, does not contain sufficient expertise in the clinical research as defined by this workshop [see below] and thus would not serve as the most suitable peer review group to review this kind of research. The workshop participants pointed out that an ad hoc initial review group in DRG was created nearly 10 years ago that was designed to review clinical oncology research. After a short time, there was a noticeable improvement in the quality of the applications. However, no one could explain why this peer review group was disbanded at the very time it appeared to be successful and needed. The factors that led to the establishment and termination of this initial review group should be determined.

"It is possible that within a short period, the downward trend in the number of clinical oncology researchers will be the rate limiting issue for translating lab findings into medical practice."

The workshop participants recommended that a study section in DRG be either realigned to consist primarily of peers who are actually doing clinical oncology research or create a new study section with this kind of charge and expertise even if it has to be done as an "experiment." The group also was very supportive of continuing the RO3 mechanism but believed NCI had unintentionally sent the research community the wrong message when the funds available to pay RO3s were so restricted.

While the PO1 [program project] mechanism has proved to be a good way to obtain peer reviewed funding for clinical studies, the funding of clinical studies is limited relative to laboratory research. It was pointed out that the successful clinical research grants are those linked to good basic laboratory research. In the opinion of workshop participants, good clinical oncology research is seldom allowed to stand on its own by the currently structured peer review groups. The peer review of these types of applications should be reassessed by NCI to ensure that clinical studies are being treated fairly relative to laboratory studies.

3. Although the clinical cooperative groups of NCI are aggressively and extensively evaluated, their focus is primarily on large scale confirmatory phase 3 studies. There appears to be a lack of encouragement for innovative clinical studies. While changes could be made to create greater flexibility in the cooperative group studies for promoting innovative clinical research, this would not have the equivalent overall positive effect of providing support to investigators for investigator initiated research. It would, however, serve to promote a higher interest level among investigators at institutions within the cooperative groups and would identify more institutional protocols that might become the basis of future group wide studies.

4. In examining the career track of a clinical researcher, the workshop participants raised an important issue addressing the existence of a critical two year gap during which the clinical research trainee must face the termination of his/her trainee fellowship support while struggling to obtain NIH grant support. The training mechanisms used by NCI should take into consideration the special time constraints that MDs must deal with.

Awardee institutions should be given greater flexibility in their use of the T32. NCI should consider the advantages of using the K12 and the individual training mechanisms such as the KO8 and K11. In addition, the KO7 should also be examined carefully to ensure that the best young MDs are encouraged to pursue careers in clinical research by providing mechanisms that may ease the financial stress during the critical two year gap. Specifically, longer training periods (from three to five years) or several consecutive mechanisms may be considered to allow young physicians, many of whom have not had previous research experience, to learn to do clinical research to the point where they can write a competitive RO1 application. . . The training mechanisms should mediate a tightly linked transition to the research support mechanisms like R29, RO1, PO1. These must be made more available to young MDs to effectively promote the transition and continuum of traineeship to independent investigatorship. Otherwise, the problems in training, retaining, and sustaining MDs in clinical oncology research will

become increasingly severe. It is possible that within a very short period of time, the downward trend in the number of clinical oncology researchers will become the rate limiting issue for translating laboratory findings into medical practice.

5. Academic institutions should find more ways to independently promote the research careers of clinical investigators. The method currently adopted by Johns Hopkins Univ. may serve as a useful model for others. In this model, the dean of the medical school controls a fund established by private donations that is dedicated to the support of research by young and clinical investigators. Such short term support enables the young clinical investigators to concentrate on the acquisition of an NIH grant within the critical two year period. Workshop participants from the cancer centers suggested that the developmental fund within the center core grant may be considered as one possible source for financial support of this nature at the discretion of the center director.

The workshop defined clinical oncology research as the investigative care of patients with cancer, which is directed toward the study of biology, diagnosis, treatment, behavioral components, and/or prevention. It often involves laboratory and preclinical research with dynamic back and forth interactions between the laboratory and the clinic, but it always is motivated by observations in patients as a result of continuously ongoing activities in direct patient care.

DCBDC Board of Scientific Counselors was cool to the study section proposals.

"The problems are much more fundamental than study sections," Margaret Kripke said. "One is that people go through medical school not prepared to do research."

"I agree," said Centers, Training, & Resources Program Director Brian Kimes. "They need special training in clinical research."

"It won't help by adding a study section," Kripke insisted.

"I realize it's a larger problem," Kimes continued. Clinical research support "is a patchwork, with no reliable way to get funds."

"There is a problem in attracting good clinical people to clinical research," board member Ross McIntyre said. "But it goes beyond creating a study section. One of the biggest problems in clinical and laboratory research is the nature of the bridge between the two." He added that cuts in research training programs "cut out people who could form the bridge."

"It doesn't do any good to emphasize training if there is no opportunity to establish careers in clinical research," Kimes argued.

"You're fingering one of the most important problems in going from basic research to the clinic," board member Albert Owens said. "In training people to do clinical research, we try to focus fundamental research right on the patient."

Board member Albert LoBuglio suggested that "if we see a real commitment by NCI to support clinical research," more physicians would be encouraged to enter the field and higher quality grant applications would be generated. "You will not do that just with a new study section."

"My arguments are reflective of the workshop," Kimes said. "You advise on whether to proceed."

"It's not worth the effort to pursue the study section issue," Kripke said. "We need to develop partnerships in basic and clinical research, and stabilize collaborative research."

"There is no argument on collaborations," Kimes said. "We want to make sure that the quality of research training is as good as basic research training."

"There is no argument that there is a problem," LoBuglio said. "I get calls every month asking, 'Do you have a good clinical scientist who can develop our clinical trials?' We want you to address the problem. We don't feel creating a new study section would do that."

McIntyre offered a motion to approve the concept provided the new study section would be broader than described in the workshop report, but the board took no action on it.

"We will proceed with the idea that we need better training as scientists [for those interested in clinical research], and we will pursue the idea of a study section which will make an effort to link clinical and basic science," Kimes said.

Freireich opened the discussion with the DCT Board of Scientific Counselors by stating that "our success in convincing the public and Congress to continue supporting cancer research is through progress, and clinical research is the key to progress. The public and Congress are more frustrated about the lack of progress than the scientific community appreciates. Young people are not being attracted to medicine. Those that are, are not being attracted to primary care; and those that are in primary care are not being attracted to oncology. We are an endangered species, and may soon be an extinct species. . . The problem with fellows focuses on security issues. It's hard to get someone to go endure the long hours and low pay for a position which may not be there. With the present

situation in NIH study sections, the physician scientist has no place to compete for funding and is frequently forced to go into the laboratory."

Kimes asked the DCT advisors for support to pursue "either realignment of a study section to make sure that clinical oncology applications are fairly and adequately reviewed, or a new study section."

Kimes acknowledged that the DCBDC board had agreed only to support realignment of a study section to focus on basic and clinical interaction. "We [staff] felt that that would only be as good as the person on the clinical end."

Board member Ralph Weichselbaum said that he felt "it would be a mistake to stack a study section." He added that when he served on the E2 study section, very few innovative clinical trials applications were submitted.

"My experience has been colored by the recent RO3 submissions," Cancer Therapy Evaluation Program Director Michael Friedman said. Those were small grants to support innovative applications of laboratory and clinical insights. Friedman said that 162 applications were submitted, mostly for phase 1 and 2 pilot studies. One hundred and twenty six were approved, and 18 were funded at a total of $1.2 million.

"It's hard to get MDs in any field involved in clinical research," Board member Paul Carbone said. "Awards are slanted to laboratory research. We're not getting the young investigator into a program of learning basic biology."

Board members Donald Kufe, William Hryniuk, and James Cox expressed support for additional efforts with the RO3 mechanism, which are reviewed by a special study section.

"I agree with nearly everything that has been said," board Chairman John Niederhuber said. "I ask that this not be for just medical oncology but as an opportunity for clinical scientists to engage in clinical oncology research. I would fight very hard for that."

Niederhuber asked NCI staff members to continue working on the proposals "and develop a scenario that we can react to: new study section, or expanded E2 study section, or more RO3s. Bring us some options at our February meeting."

DCT Board Approves New Concept For In Vivo Combination Studies

Evaluation in vivo of combination therapy for cancer treatment is the object of a new contract supported project which received concept approval at the recent meeting of the Div. of Cancer Treatment Board of Scientific Counselors.

The project, initiated by the Developmental Therapeutics Program, will cost an estimated $300,000 a year for three years.

The board also gave concept approval to recompetition of five DTP contracts involving anticancer and anti-AIDS drug development which will cost more than $22 million over three to five years. About $7 million of that will come from the amount allocated by Congress to NCI for AIDS research.

DTP decided that its preclinical pharmacology contracts for anti-HIV agents, which the board had approved for recompetition last February, could be combined the contracts for preclinical pharmacology of antitumor agents, for an estimated savings of $190,000. The board approved the antitumor agent recompetition at an estimated annual cost of $560,000; the anti-HIV agent recompetition had been approved for $910,000. An RFP for the combined contracts will be issued, with the estimated total of the two figures, funded equally from cancer and AIDS money.

The concept statements follow:

In vivo evaluation of combination therapy for anticancer activity. New contract, estimated annual cost $300,000 (100% cancer), three years.

The advantages of combination chemotherapy in the treatment of cancer have long been established in clinical practice and, in the majority of malignant diseases, multiple drug regimens are the treatment of choice. However, while combination therapy has been successful in achieving "cures" or complete responses of reasonable duration in some disease categories, there is clearly a need to identify new and more effective combination therapies.

In order to fill this need, it is proposed that a project be initiated to evaluate the preclinical in vivo antitumor efficacy of drug combinations. While combinations can be explored clinically, it would require many years and hundreds of patients to evaluate even a few promising sequencer doses of combinations. By contrast, in the preclinical setting, it is possible to test hypotheses quickly and obtain conclusive results within a relatively short time frame.

It is proposed that this project be a collaborative one, combining the preclinical expertise of DTP with the clinical knowledge and needs of CTEP. Studies would focus on combinations of newly defined interest. For example, combinations involving taxol are merited because of the recent finding of taxol's clinical activity. Also, a relatively unexplored field involves combinations of cytotoxics and biologics. Present contract funds to explore combination therapies are very limited.

Models selected for these studies will be dependent upon the compounds to be evaluated. However, tumors should be responsive to both agents under the investigation (any combination of cytotoxics and biologics) except for those occasions in which the effects of an inactive biochemical modulator on the activity of a known antitumor agent is to be explored. As appropriate, the models will utilize either murine tumors growing in immune competent mice or human tumors growing in immune deficient mice.

The initial goal of the project will be to identify drug

potentiation, i.e., instances in which drugs in combination produce a therapeutic response superior to the maximum response to either drug alone. To achieve this objective, several dosage levels of each single agent and combination will be evaluated. Additional studies may involve either confirmation in a second model and/or optimization of the antitumor efficacy of the combination through modification of either dosage ratio, schedule, sequencing, and/or timing.

Although the number of studies will be dependent on the complexity of the models utilized, it is anticipated that approximately 30 experiments may be conducted per year, e.g., 30 two drug combinations using one model and schedule or 15 two drug combinations using two models and one schedule.

Production of clinical doses of antitumor agents. Recompetition of a contract held by Ben Venue Laboratories Inc. Estimated annual cost, $1,116,300, five years (100% cancer).

This contract makes available to the Div. of Cancer Treatment a facility for the manufacturing of freeze dried and liquid filled parenteral investigational drug products. Specifically, the contractor is engaged in developmental studies of chemical agents leading to the formulation of clinical dosage forms; large scale production and packaging of parenteral dosage forms for clinical use; and assay and quality control of prepared dosage forms.

The contractor has supplied the majority of parenteral products (both freeze dried and liquid filled) in support of DCT's clinical trials. All bulk chemicals and final products are analyzed for their conformance to NCI's release specifications.

Data from final production reports are supplied to FDA as part of NCI's IND application. As a manufacturer of clinical drug products, the contractor must be registered with FDA and must comply with good manufacturing practices.

The workload for this contract is determined principally by the needs of the clinical programs, and has resulted in the contractor producing an average of over 450,000 dosage forms per year for DCT's clinical trials.

Since its inception, this contract has produced several new drugs and dosage forms of high program interest. They include taxol, trimetrexate, amonafide, fludarabine phosphate, merbarone, didemnin B, ipomeanol, echinomycin, fazarabine, ICRF-187, carboplatin, and calcium leucovorin.

Because many antitumor agents have poor aqueous solubility and stability, the contractor has had to develop several innovative techniques such as low temperature vacuum drying. This technique has been applied to several drugs with poor aqueous solubility and/or stability, and employs nonaqueous vehicles in place of water to perform the freeze drying cycle. This procedure has resulted in the successful formulation of several drugs of high interest, i.e., PCNU, diaziquone, and echinomycin.

Special procedures for handling solutions at low temperatures have also been developed, and drugs that are normally very unstable in solution may now be formulated by the use of such techniques. These procedures have been utilized successfully to produce azacytidine, mitindomide, and cisplatin.

This contractor is likely to manufacture 50 production lots annually. A single production may include the manufacture of 20,000 to 25,000 freeze dried vials or 15,000 to 20,000 liquid filled ampules.

Cultivation of marine protozoa. Recompetition of a contract held by Martek Corp. Estimated annual cost, $315,991 for three years, 100 percent funded by AIDS appropriations. NCI justified funding this entirely from AIDS money although it will continue to involve development of anticancer as well as anti-AIDS agents because it has been supported by cancer funds in the past.

Protozoa represent a taxonomically diverse group of organisms which have not been extensively investigated for their potential pharmacological properties. The wide diversity of this group, as well as the lack of information on the production of secondary metabolites by these organisms, warrants their study as potential sources of novel anti-AIDS and anticancer agents. The present contract is responsible for the cultivation of 600 cultures of protozoa representing at least 50 genera and at least two orders. These organisms are axenic or monoxenic.

The contractor furnishes to NCI 100 mg of organic extracts of each cultured organism, which are stored in the Natural Products Repository at -20 degrees C. Small samples of each extract are tested for AIDS-antiviral and antitumor activity. When significant activity is observed, the active organism is regrown on a scale sufficient to provide enough extract for bioassay guided fractionation, with a view to isolation of the active components. Stock cultures of each organism are maintained, cryogenically preserved, and delivered to NCI.

During the past year, the culture collection of protozoa continued to expand and, as of July 1, 1990, 457 cultures are on hand representing 79 genera and 11 protozoan orders. Four hundred eight of the above cultures are axenic. Two hundred sixty one of the above organisms representing 43 genera and eight orders have been cultured. One hundred thirteen extracts have been delivered to the NCI repository, and 31 of the above extracts have been tested in the anti-AIDS in vitro screen. No activity has yet been observed; however, a number of extracts have exhibited cytotoxic effects and may prove to be of interest in the antitumor screen.

It is anticipated that future projects will be conducted along the same lines as outlined in the background information above. Extracts housed in the repository will be tested for both anti-HIV and antitumor activity. It is hoped that sufficient data will become available during the next three year period to permit a meaningful assessment of the worth of this area as a source of potentially useful agents.

Analysis of anticancer and anti-AIDS chemicals and pharmaceutical formulations. Recompetition of contracts held by Midwest Research Institute, Research Triangle Institute, and SRI International. Estimated annual cost, $1,234,000 (50% cancer, 50% AIDS, five year awards.

These contracts constitute a program resource responsible for evaluating the identity and purity of bulk chemicals and formulated drug products. Reports of the analytical testing on bulk drugs and dosage forms are used as a basis for assessing the suitability of bulk drugs or finished dosage forms for use in advanced antitumor screening, toxicological studies, formulation studies, or clinical trials. These data are also supplied to the Food & Drug Administration as part of NCI's investigational new drug (IND) filings for new antitumor agents and related compounds. Historical summaries of the data are used in preparing specifications for the various bulk pharmaceutical substances, for procurement actions, and for routine quality control of these materials.

Additionally, data on solubility and stability are developed, and selected assay methods are adapted for the quantitation of drugs in plasma. The data are also provided to other contract projects to facilitate formulation development, and to aid in the analytical aspects of pharmacological and toxicological testing.

During the past calendar year, over 100 reports were received describing the analytical evaluation of separate lots of bulk drug and formulated products. Also, during the past year, analytical data from these contractors were filed with the Food & Drug Administration in support of new IND findings and amended IND

findings. Additional information has also been provided to FDA in response to requests for data following their review of various IND filings.

Data from these contractors have been supplied to other contractors responsible for formulation development, pharmacology studies, toxicology studies, dosage form production, and shelf life studies. This transfer of information facilitates the initiation of the analytical work associated with each of these projects.

It is anticipated that the major thrust of project work will continue to be as outlined in the background information above. Priority will be given to the expeditious development of analytical methods for the determination of structure and for purity assessment of new agents discovered by the new in vitro screen. At the time of recompetition, the requirements will be structured to include the analytical evaluation of both anticancer and anti-AIDS products.

Primary rodent production centers. Recompetition of contracts held by Charles River Laboratories, Harlan Sprague Dawley, and Simonsen Laboratories. Estimated annual cost, $3.4 million (80% cancer, 20% AIDS), three year awards. Since these animals are made available to investigators outside DCT, a payback system covers about $3 million of the cost.

These contracts produce approximately 2,500,000 laboratory rodents, including nude mice, annually which are distributed intramurally to NCI and NIH investigators and extramurally to NCI grantees, collaborators, and to qualified users who have expressed a strong interest in obtaining research animals whose health status and genetic makeup are of the same quality as those used by NCI. Pedigree charts for inbred and first generation hybrids are carefully maintained and monitored by the project officer. Both genetic and animal health monitoring are performed on a scheduled basis under other NCI contracts.

Essentially, the entire rodent production capacity for DCT/NCI is confined to these contracts and that at Frederick Cancer & Development Center. Although the repository for inbred strains is maintained, intramural rodent production on the NIH campus at Bethesda no longer exists. Approximately 60 rodent strains are provided through these primary rodent production centers. This program represents the sole source for several of these 60 strains. The intramural capabilities at FCRDC and the extramural production by these contracts are considered essential for the continuation of in vivo cancer research without interruption.

This resource performs a number of services that are proving very useful for investigation. For example, inquiries are often received regarding model development which requires rodent strains that are not commercially available. Such needs are met through these contracts. Intramural investigators are encouraged to utilize the off campus conventional facility operated by FCRDC to perform initial studies validating the usefulness of the model. After model validation, strains are rederived into a gnotobiotic condition through these contract resources and expanded to meet anticipated needs. These contracts have continued to serve as the base for our total rodent production program. It is estimated that approximately 85% of the rodents used by researchers on the NIH campus, as well as a large percentage of animals required by NCI funded grantees and contractors, have been supplied from this effort. Contractor usage has included the preclinical toxicological and pharmacological testing programs and DTP's extramural in vivo model development and in vivo AIDS testing programs. These production contracts were also adjusted to assist the scientific community in meeting the needs for some strains of mice during the emergency created by the disastrous fire at Jackson Laboratories.

During recent months, efforts have been introduced for the production of quantities of the severely compromised immunodeficiency (SCID) and the triple immunodeficient (BNX) strains.

These contracts will be recompeted with a renewal date effective May 1, 1992, for a three year period. These contracts will continue to provide genetically defined, pathogen free rodents, maintained under strict barrier conditions. By renewing these contracts, the many NCI research activities will be able to continue receiving quality laboratory animals, many of which are not available from any other source. Also, these contracts supply large numbers of time mated pregnant animals and dated litters to NIH campus investigators five days a week.

Preclinical pharmacology studies of antitumor and anti-AIDS agents. Recompetition of contracts held by Mayo Foundation, Ohio State Univ., and Univ. of Southern California, for anticancer agents, and the previously approved recompetition of contracts for anti-AIDS agents, held by Arthur D. Little Inc., Southern Research Institute, and Vermont Regional Cancer Center. The total combined annual cost is estimated at $1,470,000, three year awards, to be funded 50-50 from cancer and AIDS money.

This procurement will provide a continuing resource for method development and preclinical pharmacokinetic evaluation of antitumor and anti-AIDS agents under development by DTP. Active compounds identified by the in vitro HIV and human tumor cell line screens are prioritized for further study by the DCT Decision Network Committee. Task assignments will be issued to successful applicants to perform method development, pharmacokinetic, and other defined pharmacology studies on selected in vitro active agents.

Analytical methods will be developed to quantify compounds in biological fluids at levels expected to be in the therapeutic range, as estimated in vitro. The pharmacokinetics of test compounds following bolus and infusion doses will be investigated for various routes of administration in several species. Stability of agents in plasma, plasma protein binding, and bioavailability after nonparenteral administration will be emphasized.

The data obtained in these studies will be used in the planning and interpretation of preclinical therapeutic and toxicology investigations. An understanding of species similarities or differences in pharmacokinetic behavior will be useful in determining appropriate doses and schedules for detailed IND directed toxicology studies.

Since in vitro screens will be used for the initial detection of antitumor activity, pharmacologic data obtained in animals in conjunction with preclinical therapeutic studies in mouse tumor models will be important for extrapolating effective in vitro and in vivo concentrations and exposure times to rational doses and schedules in phase 1 clinical trials.

NCI To Evaluate Chernobyl Accident Effects On Soviets' Thyroid Function

NCI has signed an interagency agreement with the Dept. of Energy for evaluation of the effects of the Chernobyl nuclear reactor accident on the health of citizens of the Soviet Union.

The agreement will transfer $100,000 from DOE to the Div. of Cancer Etiology to coordinate U.S. efforts to work with Soviet counterparts "to evaluate the effects of the Chernobyl reactor accident on thyroid dysfunction of Soviet citizens, develop a protocol for

assessing the leukemia incidence and consider the feasibility of conducting child and adult health surveys," according to the agreement.

DCE Director Richard Adamson said he has assigned Bruce Wachholz, chief of the Radiation Effects Branch, to be responsible for implementing the agreement and coordinating U.S. efforts and interaction with the Soviets. Wachholz has "extensive experience and familiarity with all aspects of fallout studies," Adamson said.

The effort grew out of a bilateral U.S.-USSR agreement signed in April 1988 to cooperate in civilian nuclear reactor safety. The agreement, signed by the U.S. Nuclear Regulatory Commission and the USSR State Committee for the Utilization of Atomic Energy, includes the investigation of health effects and environmental protection relating to nuclear reactors, and specifically the study of the health consequences of the Chernobyl accident.

'Delicate Undertaking'

"This is a very delicate undertaking, both scientifically and politically, and will require extensive interaction with numerous other organizations involved with studies in the Soviet Union," Adamson told the DCE Board of Scientific Counselors at its recent meeting.

"We look upon it as an opportunity to see whether there would be a useful purpose served in entering into a collaborative long term follow up study with the Soviets."

Clinical Epidemiology Branch Chief Robert Miller and Gilbert Beebe, also of the CEB, visited the Soviet Union in 1989 on a DOE-organized trip, after which DOE asked them to explore the possibility of follow up studies on leukemia and thyroid disease.

Beebe recently returned from a trip to Kiev and Minsk to prepare for a U.S.-USSR workshop on leukemia to be held in the U.S. next year.

Two Ukrainians visited the U.S. to arrange a joint workshop on thyroid disease to be held this December near Kiev.

The U.S. delegation for the thyroid meeting includes Wachholz, Beebe, DCE board member Roy Shore, Andre Bouville of the Radiation Effects Branch, and Jack Robbins and Jan Wolf of the National Institute of Diabetes & Digestive & Kidney Diseases.

The schedule for the interagency agreement calls for a U.S. evaluation of the potential for long term follow up studies in the Ukraine, in Byelorussia and/or in the Russian Federation, with NCI making a recommendation by the end of 1991 to the DOE and Nuclear Regulatory Commission on the feasibility of initiating such studies.

DCE Board Approves Recompetition Of Human Tissue Procurement

NCI's Div. of Cancer Etiology Board of Scientific Counselors gave unanimous concept approval to recompetition of a contract for procurement of human tissues, as well as five other non-competitive contracts.

Following is the concept statement for the recompetition:

Resource for procurement of human tissues from donors with an epidemiologic profile. Recompetition of contract held by Georgetown Univ. Medical School. Total funding proposed $356,763, proposed first year award $84,014; four years.

The Laboratory of Human Carcinogenesis investigates mechanisms of carcinogenesis directly in human tissues and cells. The laboratory requires continuing sources of human materials from organs considered the primary targets for human cancer--bronchus, lung, colon, pleural mesothelium and exudate fluids and cells from the lungs of hospitalized patients and healthy volunteers.

The materials obtained are used in developing and employing model systems for studying mechanisms in carcinogenesis, to establish biochemical markers associated with early stages of cancer and for detection of individuals at risk for developing bronchial and colorectal cancer.

The successful offeror is required to obtain approval for the project from the local IRB monitoring the protection of human subjects. The offeror must obtain the cooperation of the surgery and pathology departments and the pulmonary diagnostics service to contact patients and other volunteers for informed consent to collect residual, diagnosed tissues and blood and lavage samples, to review the medical charts and administer a questionnaire for medical, personal and occupational histories.

The design includes:

1) collection of preoperative medical histories and subsequently, nontumorous and tumorous lung, bronchus, colon and pleural mesothelium at the time of surgery or autopsy, 2) diagnostic and microscopic characterization of the tissue specimen; 3) bronchial lavage for alveolar macrophages and venous puncture for peripheral blood lymphocytes, red blood cells and sera from smoking and nonsmoking healthy and patient volunteers, 4) transport of tissues to LHC and 5) administering an LHC questionnaire to provide personal history data on donors.

The other, noncompetitive contract concepts and the total amounts obligated were:

--Cellular and molecular studies of human hepatocarcinogenesis in China, total $180,000.

--Bilogical specimen repository for patients at high risk for cancer, total $1.354 million.

--Studies of the epidemiology of potentially oncogenic and immunosuppresive viruses in West Africa, total $135,000.

--Population based natural history study of cervical neoplasia in a high risk region of Latin America, total $857,000.

--The NHANES I epidemiologic follow up study: 1991 phase, total $200,000.