THE CANCER LETTER

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

Vol. 18 No. 25
June 19, 1992

Price $215 Per Year US, Canada.
$240 Per Year Elsewhere

Bristol-Myers Runs Afoul Of FDA In Attempt To Distribute Chapters Of Oncology Textbook

Principles and Practice of Oncology is hardly a controversial book. Its authors, Vincent DeVita, Samuel Hellman and Steven Rosenberg are established figures in oncology. With 30,000 copies sold over the past four years, the 2,600-page textbook cannot be called obscure.

Could any harm come from a drug company distributing selected chapters of this book to physicians?

(Continued to page 2)

In Brief

NCI Receives Two Proposals For Antineoplaston Trials, None For Children; Stubbe Elected To NAS

TWO LETTERS of intent were received by NCI from investigators proposing to undertake clinical trials of "antineoplaston," an unconventional drug available at the Texas clinic of **Stanislaw Burzynski** (**The Cancer Letter,** June 5). Following the June 1 deadline for proposals to take part in NCI's three adult trials and a pediatric trial, NCI received no proposal for the pediatric trial, said David Parkinson, acting chief of the Investigational Drug Branch. "We will be reviewing these in the next week or two as for their suitability," Parkinson said of the two proposals. "No trials will start until the drug has met the Good Manufacturing Practices standards, and both NCI and FDA have had a chance to review the material." . . . **JOANNE STUBBE**, Massachusetts Institute of Technology, has been elected to the National Academy of Sciences. Stubbe, a member of NCI's Div. of Cancer Treatment Board of Scientific Counselors, is an expert in the metal catalysis of biochemical reactions. . . . **MICHAEL GREVER**, director of NCI's Developmental Therapeutics Program, has been appointed to the NIH Senior Executive Service, making his DTP appointment official. . . . **PATRICK MAZIER** succeeded **Robert Beart** as president of the American Society of Colon & Rectal Surgeons at the society's annual meeting in San Francisco last week. . . **RONALD HERBERMAN**, director of the Pittsburgh Cancer Institute, received the Institute for Advanced Studies in Immunology & Aging Lifetime Science Award in recognition of his work on cells of the immune system . . . . **DAVID LIVINGSTON**, director and physician-in-chief of Dana-Farber Cancer Institute, was named the first recipient of the Emil Frei III Professorship in the Faculty of Medicine at Harvard Medical School. Frei served as DFCI director and physician-in-chief from 1973 to 1991, and now is physician-in-chief emeritus and chief of the Div. of Cancer Pharmacology.

FDA Declines Company's Request To Distribute Portions Of Textbook

(Continued from page 1)

When Bristol-Myers Squibb Co. asked the Food & Drug Administration's permission to reprint a five-chapter portion of Principles and Practice, the agency said no.

"At this time, the above item is considered unacceptable," FDA wrote. "The excerpted textbook contains chapters which discuss unapproved indications of Bristol-Myers Squibb oncology products. "The entire, unaltered textbook could possibly be distributed as a 'service' of BMS, assuming that discussions of uses of BMS drugs do not constitute a major portion of this book," the letter continued.

A copy of the letter, dated March 23 and signed by regulatory review officer Heidi Marchand, was obtained by **The Cancer Letter.**

"Bristol-Myers Squibb is the biggest manufacturer of oncology products in the world," said Peg Forster, an official with the book's publisher, J.B. Lippincott Co. "If our book did not cover their therapies, then it would not be a good book."

First Amendment Issue?

Bristol's plan was to commission the printing of a 107-page section of the book, covering lung cancer surgery, radiation therapy, chemotherapy and pulmonary complications of cancer.

The chapters were to be reprinted in their entirety and distributed to pulmonologists, specialists who ordinarily would not have bought the $180 book. Altogether, 5,000 copies were to be printed, said Forster, director of Lippincott Health Care.

According to Forster, Lippincott and FDA were planning a telephone conference and a meeting in an attempt to resolve their differences.

Commenting on the controversy, FDA spokesman Mike Shaffer said the issue is restriction of advertising, not restriction of free speech.

"The law under which FDA operates is very clear and very explicit in terms of stating that firms are not allowed to promote unapproved uses. I can't imagine why there would be freedom of speech issues here," Shaffer said.

"We are not preventing the dissemination of information. We are just preventing the firm from becoming involved in dissemination of information which constitutes promotion. That's a totally different issue."

In recent months, FDA has been cracking down on the drug companies' promotional materials and the companies' role in continued medical education.

"We know that some companies have used ostensibly open medical education programs to disseminate selected and misleading information about drug products or to promote specific products, including off-label uses of those products," Michael Taylor, FDA's Deputy Commissioner for Policy, said in a recent speech.

"The critical element in non-promotional continued medical education is 'independence,'" Taylor said. "It has long been FDA's position that company supported CME whose content--other than the selection of general topics--is independent of the company's control can be considered nonpromotional and thus not subject to FDA regulation."

Books vs. Gifts & Travel

"Independently produced textbooks is precisely the kind of information FDA should encourage dissemination of," said Alan Bennett, an attorney with Fox, Bennett and Turner, a Washington firm that represents Bristol-Myers Squibb.

"Surely FDA would concede that it is far better for pharmaceutical companies to distribute independently produced textbooks containing the latest scientific information than it is to provide gifts or travel," Bennett said to **The Cancer Letter.**

"FDA always maintains that the law requires these restrictions and there are no First Amendment issues involved. Well, it doesn't and there are."

In a letter to FDA, Lippincott's president and CEO Alan Edelson, wrote that Principles and Practice cannot be considered promotional.

"I sympathize with your effort to root out misnamed 'independent' medical publications that have actually been funded by the pharmaceutical industry," Edelson wrote in the May 13 letter.

"However, chapters from our textbooks are produced independently of the pharmaceutical industry and cannot be considered in the same

THE CANCER LETTER

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

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

Subscription rate $215 per year North America, $240 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

category as these other publications.

"Each chapter in the Principles and Practice of Oncology text is written by a different contributor and meant to stand on its own apart from the text, hence excerpting chapters cannot be considered taking this material out of context. By prohibiting the distribution of these five chapters from the book, you imply that Drs. DeVita, Hellman and Rosenberg and their contributors are somehow influenced in their writing by Bristol-Myers Squibb...

"It is wholly illogical to assert that information which is scientific and rigorous when distributed by one party can become damaging to the public interest when it is redistributed, word for word, by another party.

"If your intention is truly to restrict the redistribution of our books by our customers, that raises a major issue which goes far beyond the FDA, and which we cannot allow to go unaddressed. Indeed, the First Amendment issues which are ignited by such a policy would have to be raised with other appropriate parties."

NCI, Rhone-Poulenc Sign Agreement For Trials, Development Of Taxotere

NCI and Rhone-Poulenc Rorer Inc. have signed a Cooperative Research and Development Agreement for the joint development of taxotere, the promising anticancer agent that is a partly synthetic version of taxol, derived from the bark of the Pacific yew tree.

Under the agreement, a steering committee made up of NCI and RPR staff will plan trials that are to be done jointly. The company holds a Investigational New Drug application from the Food & Drug Administration for clinical trials of the compound.

The agreement with NCI stipulates that the company will cooperate on additional clinical trials of taxotere in ovarian cancer, adult acute leukemia, pediatric solid tmors and leukemias, untreated small cell lung cancer, melanoma, non-Hodgkin's lymphoma, soft tissue sarcoma, and cancers of the stomach, prostate, baldder, cervix, and head and neck.

These studies will complement the company's ongoing phase 2 clinical trials with taxotere in breast, ovarian and colon cancer in the U.S. and Europe.

Representatives from the company and the NCI steering committee, and NCI's network of investigators around the U.S., will conduct the clinical trials, and the company will have exclusive rights to the data obtained in these trials.

The company has an agreement with the Japanese firm Chugai for development of the agent in Japan.

The CRADA was signed May 14, but an official announcement has not been made. The Institute and the company reportedly are negotiating over wording of a press announcement.

Unlike taxol, which is being developed under a separate CRADA between NCI and Bristol-Myers Squibb Co., taxotere is patented. Rhone-Poulenc Rorer holds several U.S. patents on the compound, which is made from the taxol precursor, baccatin III.

The company will provide taxotere for the joint trials and, if appropriate, for compassionate use, NCI sources said.

DCE Advisors OK Ovarian RFA, Four Other New Grant Programs

Advisors to NCI's Div. of Cancer Etiology have given concept approval to a new program that would set aside $2 million in fiscal 1993 to fund five-year grants in the epidemiology of ovarian cancer.

The DCE Board of Scientific Counselors unanimously approved the new program, which was recommended by participants of a workshop held last September to discuss promising research directions in the epidemiology and etiology of this malignancy, which killed approximately 12,000 U.S. women in 1990.

The board also gave unanimous concept approval to four other new grant programs, setting aside $3.5 million for fiscal 1993 to fund research grant applications.

In addition, the board gave concept approval to recompetition of a $9.5 million, five year contract for support services for radiation-related studies, and two new procurement programs.

Following are the concept statements:

Reports on concept reviews by the boards of scientific counselors of NCI divisions provide readers with advance notice of the Institute's spending plans which will show up in announcements for Requests for Proposals, Requests for Applications, or Program Announcements in subsequent months. These will be published in ***The Cancer Letter****; until that time, proposals need not be written.*

Epidemiology of Ovarian Cancer. Concept for a new RFA, first year funding $2 million, five years. Program Director: A. R. Patel, DCE Epidemiology & Biostatistics Program, Extramural Programs Branch.

Ovarian cancer is the most lethal gynecologic malignancy. On a worldwide basis, it is estimated that over 140,000 cases are diagnosed annually, representing over 4% of all cancer cases in women. In the U.S., incidence and mortality estimates for 1990 indicated that approximately 20,500 new cases were diagnosed

and 12,000 women died. Overall, the probability that a woman will be diagnosed with ovarian cancer in her lifetime is 1 in 70. The incidence rate is currently 46% higher in whites than in blacks. The incidence of ovarian cancer seems to have decreased slightly since 1973, but the survival rate has changed very little. Survival is related to age. During the period 1981-86, women diagnosed prior to age 65 had a five-year relative survival rate of 48% compared to 24% for those diagnosed at age 65 or older.

The highest ovarian cancer rates are reported from industrialized countries with the exception of Japan. The age-adjusted mortality rates are 1.69, 3.02, 7.04 and 11.02 per 100,000 for Japan, Italy, U.S. and Denmark, respectively. Japanese migrants to Hawaii and their first generation offspring have a higher incidence of ovarian cancer than women in Japan, suggesting environmental influences. The trends in ovarian cancer over the last two decades indicate increasing rates in low-risk areas such as Japan and Singapore.

The purpose of this initiative is to stimulate innovative epidemiologic research into the origins of ovarian cancer. Collaborations of multiple disciplines and research institutions are particularly encouraged. Potential applicants will be encouraged to submit Interactive Research Project Grants. Whenever possible, research designs should make use of existing resources, such as familial ovarian cancer registries and specimen repositories. Projects will be evaluated on their potential for enhancing the understanding of ovarian cancer etiology and means of prevention.

The initiative permits a range of epidemiologic and interdisciplinary investigations of ovarian cancer including, but not limited to:

1. Epidemiologic studies of:

--the long-term effect of combination oral contraceptives, with special reference to age at initial use, and age at cessation of use, on ovarian cancer risk by pathologic type;

--the relationship between hormone replacement therapy and ovarian cancer risk;

--the use of fertility-promoting drugs, ovarian stimulants or in vitro fertilization in relation to ovarian cancer risk;

--the interrelationship of tubal ligation and hysterectomy, hormone levels, and ovarian cancer risk;

--the association of unilateral oophorectomy, age at oophorectomy, and ovarian cancer risk;

--the influence of diet and physical activity and their interaction on ovarian cancer risk;

--the relationship of exposure to potential oocyte toxins such as talc, galactose, caffeine, smoking and other agents to ovarian cancer risk among women who use and those do not use oral contraceptives.

2. Molecular epidemiology studies exploring differences in genetic predisposition to ovarian cancer due to variations in susceptibility genes, hormone metabolism, DNA repair activities, chromosome sensitivity to mutagens or other factors.

3. Analytic studies of ovarian cancer to determine the impact of changes in exposure due to migration from low- to high-risk regions and/or to secular changes in lifestyle and environment.

4. Studies of racial/ethnic differences in the histologic and cytologic parameters of ovarian cancer that may reflect differences in exposure or susceptibility.

5. Population-based studies of the correlation of estrogen and progesterone receptor content of ovarian tumors with histologic type, grade, clinical prognosis, and exposure history.

Possible Role of Metallothionein in Carcinogenesis. Concept for a new RFA, first year funding $1 million, four years. Program Director: Yung-Pin Liu, DCE Chemical & Physical Carcinogenesis Program, Chemical & Physical Carcinogenesis Branch.

Metallothioneins (MTs) are a family of low molecular weight, cysteine-rich, heavy metal-binding proteins. The mammalian forms have 61 amino acids, including 20 cysteine residues, but no aromatic amino acids or histidines. The metal content of purified MT is highly variable and depends on the organism, tissue, and history of heavy metal exposure. For example, MT isolated from human liver autopsy samples contains almost exclusively zinc (Zn) whereas MT from kidney contains substantial levels of cadmium (Cd) and copper. These differences probably reflect both the natural heavy metal exposure of the organs and the expression of different MT isoforms. The synthesis of MT in animals is induced in a variety of ways, including exposure to heavy metals, physiologic stress, and changes in endocrine status, and requires increased transcription of MT genes. Our knowledge of MT degradation, however, is somewhat limited. In vivo experiments have suggested that the rate of MT turnover in the cytosol fraction is influenced by the specific metal bound to the polypeptide. The disappearance of 35S-labeled MT from the cytosol fraction reflects degradation of this protein by lysosomal proteases since apometallothionein (without metal), Zn-MT and Cd-MT were rapidly degraded in lysosomal extracts. To date, our understanding of the function of MT has been focused on its role in metal transport, mineral nutrition metal detoxification and detoxification of other chemicals.

The objectives of the proposed RFA are designed to encourage research to elucidate the possible role of MT in carcinogenesis. Specific topic areas that might be supported: (1) Biological and toxicological roles of MT. Studies such as metal homeostasis, detoxification, transport, role in cell proliferation during the perinatal period, and involvement of Zn as a second messenger in signal transduction, as related to cellular normality. (2) Regulation of MT gene expression. Studies of metal induction in various tissues, during development, and organismal specificity in transgenic and model systems and i normal versus transformed cells. (3) Role of MT in tumor cell pithobiology. Studies to define the role of MT in tumor cell progression and metastasis and the types and staging of tumors that may or may not express excess MT. Studies directed at enhancing a rational basis for therapeutic intervention with metallic anticancer drugs. (4) Role of MT in cancer chemotherapy. Studies on the role of MT in tumor cell resistance to anticancer drugs, especially metal based drugs. Studies on the use of induction of MT in nontumor tissue as an adjunct to reduce toxicity for metallic chemotherapeutics. Studies involving mechanisms by which MT synthesis could be specifically depressed in tumor cells to make them hypersusceptible to metallic chemotherapeutics. (5) Susceptibility factors in metal carcinogenesis. Studies assessing MT gene expression in target tissues of metallic carcinogen in rodents and molecular epidemiology of MT with special emphasis on target tissues of metallic carcinogens in humans (e.g. prostate, lung). (6) Molecular interaction of MT with ligands (metals and anticancer drugs) binding and exchange; structural and dynamic studies.

Since these research objectives cut across the traditional administrative divisions of NCI, it is proposed that a joint RFA be issued soliciting R01 applications to address these topics. The issuing program would be the Chemical and Physical Carcinogenesis Branch in DCE. In addition, two other NCI divisions would be sponsors of this RFA. Both the Cancer Biology Branch, Div. of Cancer Biology, Diagnosis, & Centers, and the Grants and Contracts Operations Branch in the Developmental Therapeutics Program, Div. of Cancer Treatment, have expressed interest in a collaborative announcement. Applications would be assigned to the most relevant sponsoring program and would be reviewed by a special study section. A joint funding plan would be developed after the review is completed.

The Regulation, Function and Specificity of Proteins Induced in Mammalian Cells Exposed to Ionizing Radiation. Concept for a new RFA, first year funding $1 million, four years. Program Director: R.A.Pelroy, DCE Chemical & Physical Carcinogenesis Program, Radiation Effects Branch.

In the late 1980s it was discovered that exposure of mammalian cells to ionizing radiation induces the differential expression of a set of proteins (i.e., radiation-modulated proteins or RMPs) which are part of a complex radiation-induced-stress response in both human and rodent cell lines and in vivo in rodents.

The purpose of this proposed RFA is to stimulate basic research on the function, regulation and specificity of proteins that are differentially expressed in mammalian cells exposed to ionizing irradiation. Priority areas of research should include but not be limited to:

--the use of advanced analytical techniques to identify, isolate and clone cDNAs and structural genes for the radiation-specific RMPs into reference libraries and the development of vectors suitable for the expression of the cloned genes in mammalian cells of different radiosensitivities and DNA-repair capabilities;

--identification and structural analyses of ionizing radiation-induced DNA binding proteins and the corresponding DNA-regulatory elements that govern expression of the structural genes for the radiation-specific RMPs;

--molecular-level studies of the pathways of signal transduction from the introduction of critical radiogenic lesions to the differential expression of the radiation-specific RMP structural genes.

In more general terms, work supported by the RFA will seek to define the relationships of the uncharacterized RMPs to well-established phenomenological endpoints induced by exposure of mammalian cells to ionizing radiations such as G2-arrest, general cessation of DNA-synthesis and gene expression, radiation-specific DNA-repair (e.g., potential lethal damage repair) and radiosensitivity. The mechanistic basis for these radiologic endpoints is poorly understood at the molecular level although they are important factors in determining levels of radiation-induced mutagenesis, neoplastic transformation and survival. Finally, much of the work with radiation specific RMPs to date has used low-linear-energy-transfer (LET) x-rays and gamma rays. Little comparable information is available on the efficacy of high LET irradiation (e.g., alpha particles, neutrons) on the induction of specific sets of proteins. The RFA therefore encourages studies where the effects of exposure to low- and high-LET forms of irradiation can be compared.

Support Services for Radiation and Related Studies. Recompetition of a contract held by Westat Inc. Total award $9.5 million over five years. Project officer: John Boice, Epidemiology & Biostatistics Program, Radiation Epidemiology Branch.

Studies of populations exposed to ionizing radiation are being conducted to strengthen the quantitative basis for risk estimation, especially at low-doses, to improve understanding of the role of host and environmental factors on radiogenic risk, and to provide insights into carcinogenic mechanisms, including the integration of new laboratory approaches. In addition, studies are conducted to assess the late health effects in patients treated with cytotoxic drugs in combination with radiotherapy.

This contract establishes a mechanism to provide all of the support services required to conduct a wide variety of field studies. While the scientific direction and overall supervision for all projects is the responsibility of the professional staff of the Branch, support services provided by the contract include the development of liaison with organizations and individuals at a local or international level whose cooperation is needed for the conduct of a study; the design and development of forms required to conduct field investigations (interview forms, record-abstracting forms, interviewer manuals, etc.); the hiring, training, and supervision of technical personnel (interviewers, record abstractors, and persons to collect and arrange transport of biological specimens; the actual collection of the required data; the tracing of individuals, obtaining either a current address or death certificate; and the data reduction activities involved in field investigations (e.g., coding, keying, editing, and a variety of data processing activities). The contractor also must provide field supervision and develop quality control mechanisms to ensure the quality of the activities as well as the maintenance of control of all aspects of each study by the appropriate Branch investigators.

Support activities have been applied in one of three general ways. In some studies, the contractor is responsible for virtually all field activities required to complete a study. This generally occurs when the study is conducted in several areas, or with collaborating institutions that have none of these necessary capabilities. A second manner in which the contractor assists is by providing only selected types of support activities that cannot be accomplished by the locally-based collaborators. Examples of this include forms development, interviewer training, random-digit dialing for control selection in areas where such activities are not often conducted, or tracing subjects for vital status using national resources. Finally, the contractor may act as a coordinating center for multi-center collaborative studies. In these circumstances; in addition to providing support services, the contractor assists in monitoring and implementing the standardized application of the study design across the different centers.

In addition to core personnel who are committed to the support service contract, the contractor is expected to expand or reduce staff to meet the varied and changing requirements of the Branch program. Currently, there are 5 study managers, 3 computer support staff, 15 medical and other coders, 2 coding supervisors, and 9 telephone tracers in support of the overall program of studies. There have been as many as 10 interviewers and 6 abstractors in the field as needed to support research activities.

This project will provide support services for the conduct and management of epidemiologic investigations of cancer directed by the Radiation Epidemiology Branch alone or in collaboration with other investigators. The principal activities can be classified as follows: 1) liaison, whereby the contractor assists in the coordination of multi-center studies and helps facilitate cooperation between NCI and its collaborators; 2) development of study materials, including questionnaires, abstract forms, coding forms, manuals of field procedures, and other documents; 3) identification of study subjects, including location of cancer patients and/or their relatives, selection of controls through such methods as random-digit dialing, and acquisition of appropriate study population rosters or files; 4) training of interviewers, abstractors and other field personnel; 5) field supervision and management; 6) interviewing of study subjects; 7) abstracting and coding relevant medical and other records; 8) obtaining biologic specimens and arranging for appropriate laboratory tests by designated laboratories; 9) data preparation and processing, including editing and preparing information in a format suitable for computer analysis; and 10) quality control and standardization, to ensure that appropriate and valid data are obtained.

Throughout the development of the use of support services contracts to assist in field research, we have been very attentive to the need for quality control measures to ensure that Branch epidemiologists were in control of all scientific aspects of each project. In addition to frequent telephone contact, contract

personnel meet weekly with Branch investigators, and both staffs meet monthly for overall review, resolution of outstanding problems, and setting of priorities. Detailed monthly reports are written by the contractor, describing progress on a study-by-study basis, and are critiqued monthly in writing by NCI investigators. All individual steps undertaken in a study are documented by the contractor, including a log of decisions made which affect study design, conduct or analysis. Verifications, discrepancies and error rates for data collection, preparation and entry are reported to Branch investigators. Branch members accompany contract personnel to field operations and frequently participate in pre-testing of data collection forms, evaluation of quality of medical or other records, and the quality control re-abstraction or re-interviewing process. Annual site visits are conducted to evaluate further contract personnel, resources, and performance. The need for quality control measures was an issue focused on during site visit evaluations. It was noted that an "impressive quality assurance program is built into these contracts" and that "the issue of quality assurance within the support service contracts seems to be well addressed."

A Case-Control Study of Osteosarcoma. Concept for a new contract (RFP), total award $800,000 over four years. Project Officers Robert Hoover, Allan Hildesheim, DCE Epidemiology & Biostatistics Program, Environmental Epidemiology Branch.

Osteosarcoma is a mesenchymal malignancy of the bone that occurs at a rate of three per million per year in the U.S. It occurs most frequently at the growing end of bones and displays a bimodal age incidence, with one peak occurring in adolescence and the other in those aged 55 and over. It accounts for about one-third of all bone tumors, is 1.4 times more frequent in males than in females, and occurs at a similar rate in blacks and whites. The etiology of osteosarcoma is unknown. The adolescent age peak, the excess in males, and the finding of increased incidence in giant breeds of dogs compared to that in small or medium-sized dogs suggest a direct relationship of risk with growth rate of bones, at least among the young. However, two small analytic studies have found conflicting results with respect to pediatric growth curves for cases and controls. The only established environmental risk factor for osteosarcoma is high doses of ionizing radiation. The malignancy has been induced by radium-226 in women involved in painting radium dials on watches and by radium-224 used in the treatment of tuberculosis of the bone. Radiation therapy involving exposures to thousands of rads also has been linked to osteosarcoma.

However, numerous studies of lower levels of radiation, including exposures to hundreds of rads have not identified excesses of osteosarcoma. Laboratory studies have linked exposures to chemical carcinogens (e.g., vinyl chloride, cytotoxic drugs, aflatoxin) to osteosarcoma development in rodents and monkeys. These clues have gone largely unexplored in humans except for the observation of increased risk of osteosarcoma following alkylating agent treatment for childhood cancer. A variety of lines of laboratory evidence has also pointed to a potential role for an oncogenic virus. Although limited in scope, observations in humans have not revealed evidence of an infectious spread of bone cancer. Case reports of osteosarcoma appearing at sites of previous trauma, in conjunction with metallic implants, and among caisson workers who develop bone infarcts as a result of exposure to compressed air conditions have all raised a suspicion of a relationship of this tumor with trauma. However, no systematic evaluation of this hypothesis has been conducted.

The objectives of this procurement will be to augment an ongoing multicenter, case-control study of osteosarcoma in order to:

1. Assess by questionnaire the full range of possible risk factors suggested for osteosarcoma, and to assess these factors for the entire age range of patients.

2. To sample unaffected bone of cases and two control groups (other bone tumors and an autopsy series) in order to evaluate cumulative fluoride body-burden as a risk factor.

3. To collect blood samples from cases and controls and tumor specimens from cases to assess the potential role of mutations in the p53 and Rb genes in the development of these tumors.

The ongoing study has both a retrospective (last three years of well as a prospective (next 3 years of cases) component. We propose to augment the prospective component only with the following measures:

1. Expand the age range to include all cases; this would yield a trial sample size of 480 cases.

2. Develop and administer a questionnaire to assess all of the areas of potential risk factors.

3. Identify two control groups in addition to the hospital controls for the ongoing study. One control group would be patients with other bone tumors and one would be an autopsy series. Both control groups would be matched to the cases on age, sex, race, hospital, and distance of residence from hospital.

4. Obtain iliac crest biopsies from all cases and other tumor and autopsy controls, and preserve them in an appropriate manner for pathology and laboratory assays.

5. Obtain blood samples from cases and controls and preserve them in an appropriate manner for indicated laboratory assays.

Transfer of Theoretical Biostatistical Methodology to Epidemiologic Studies of Cancer. Concept for a new RFA, first year funding $500,000, three years. Program Director: Marthana Hjortland. Epidemiology & Biostatistics Program, Extramural Programs Branch.

The purpose of this proposed RFA is to stimulate interactions among theoretical and applied biostatisticians, cancer epidemiologists, computer scientists and programmers, and to promote the introduction of appropriate theoretical methods to epidemiologic projects in cancer research. In most instances these grants will be small addenda to approved biostatistical or epidemiological R01 grants. This initiative proposes to link peer-approved activities to provide a mechanism for facilitating the transfer of new biostatistical methodologies to applied biostatisticians and epidemiologists. The goal is to assure the validation and integration of promising new statistical and computing techniques into epidemiologic studies. Projects funded by this initiative will lead to substantial cost savings by developing computer programs and analytical techniques that can be shared by numerous projects. We will particularly encourage research relevant to studies or data sets on cancer, especially breast, ovarian, prostate and/or cervical cancers.

This mechanism should permit a wide range of small projects that might be used by Master's and PhD level biostatisticians and epidemiologists to tailor and apply new biostatistical designs or methodology for use in specific cancer projects. There are many possible approaches, two of which are: 1) biostatistical consultation on an epidemiologic study that compares the use of conventional statistical procedures to theoretical methodology of greater applicability to epidemiologic cancer research, and 2) development of an expository application for cancer research of theoretical statistical methodology from a dissertation or publication, under the tutorship of the dissertation advisor or with the collaboration of the publication's authors.

The outcomes of these projects could include published articles on the translation of methodologic theory into

computationally feasible techniques, presentations at scientific meetings, lecture notes, or efficient, well-documented and well-written codes for user-ready computer programs/functions that can be made available to the scientific community. (It is not the intent of this initiative to fund the development of commercial programs or packages.) Subjects of interest include, but are not limited to: Cox regression model, logistic regression model, ordered logistic regression, polychotomous regression model, sequential trials, group sequential trials, multiple endpoints, surrogate endpoints, time-dependent covariates, censored data, left and right truncation, meta-analysis, data augmentation methods, Martingales (counting processes in survival analysis), frailties, repeated measures, and determination of maximum tolerated dose.

Biotechnology Transfer to Epidemiologic Studies: Molecular/Biochemical Epidemiology. Concept for a new RFA, first year funding $1 million, three years. Program Director: K. Iwamoto, DCE Epidemiology & Biostatistics Program, Extramural Programs Branch.

A large proportion of human cancers are thought to be attributable to environmental factors, some of which may interact with host susceptibility states. The problem of identifying the effects of specific risk factors and evaluating their relative importance is a challenging one. Multiple exposures to a variety of agents over extended periods are the rule rather than the exception, and many populations are exposed to low levels of carcinogens. A wide range of susceptibility mechanisms may be involved in processes of carcinogenesis, and the long latency period of many cancers may make cause-effect relationships elusive.

The goal of this initiative is to encourage and stimulate epidemiologic investigations designed to validate and apply biomarkers of exposure or susceptibility for research in cancer etiology. For biomarkers demonstrated to have utility, assessment of the extent of intra- and interindividual variability is important. Validation procedures should consider determinations of range of normal values, as well as sensitivity, specificity, and predictive value. The influence of biological variables such as age, sex, race, ethnicity, nutritional status, preexisting disease, and lifestyle should be addressed.

Inter-institutional collaborations between laboratory scientists from multiple disciplines and epidemiologists are encouraged to promote integrated planning of study protocols and experimental methods as well as conduct of research. Extension of an ongoing epidemiologic study by the addition of a laboratory component can be proposed. Whenever possible, research design should utilize shared laboratory and specimen resources. Ease of study conduct and expense, as well as collection, storage, and transport problems should be considered. Projects will be evaluated on their potential for enhancing the understanding of cancer etiology and strategies for prevention. We particularly encourage studies with relevance to breast, ovarian, prostate and cervical cancers.

The initiative permits a range of epidemiologic investigations, relevant to cancer etiology, including, but not limited to:

--Demonstration of the feasibility of developed biomarkers for epidemiologic research (e.g., heterocyclic amine food mutagens, benzene-I thymine glycol, mutation of the hypoxanthine guanine phosphate transferase (HGPRT) gene);

--Validation of biomarkers in exposed and unexposed population subgroups (e.g., ethnic and minority populations, family units, occupational cohorts, patients taking chemotherapeutic agents or other medicinal compounds);

--Determination of levels of agreement of mutually confirmatory methods of analyses for measuring the same biomarker (e.g., DNA adducts by physicochemical, immunoassay, and postlabelling methods) with consideration of inter- and intra-laboratory variability;

--Comparison of biomarkers or combinations of biomarkers in different sources of specimens such as human cells, tissues, organs, and body fluids;

--Determination of specific sampling conditions (e.g., timing, seasonality, repetitive or serial testing) including host/environmental factors with/ without interactions (e.g., dietary, viral, hormonal) that may influence validity, reliability, and reproducibility;

--Establishment of background or reference levels in normal or unexposed populations (e.g., cytochrome P450 isoenzymes, glucuronyltransferase, covalent RNA or protein adducts, arylamine-macromolecular adducts).

Indoor Radon, Diet, and Lung Cancer Risk Among Women. Concept for a new contract (RFP), total award $1.82 million ($1.52 million from NCI; $300,000 from EPA), for four years. Project Officer: Michael Alavanja. DCE Epidemiology & Biostatistics Program, Radiation and Environmental Epidemiology Branches.

Cigarette smoking is recognized as the leading cause of lung cancer in the United States. However, a sizable number of cases occur each year which are not attributable to smoking; thus, it is important to identify and quantify these other causes. In recent years, exposure to radon in the home and dietary factors have emerged as potentially significant environmental lifestyle exposures of importance in the etiology of lung cancer.

Objectives of this project are:

1. To evaluate the possible link between radon exposure in the home and lung cancer, and if found to examine the nature of the dose-response relationship. In comparison with an ongoing study of nonsmoking women we will evaluate, indirectly, whether cigarette smoking modifies the effect of radon exposure in the home.

2. To evaluate the possible relationship between dietary factors and lung cancer. The possible effects of cooking practices will also be evaluated.

Approximately 700 women newly diagnosed with lung cancer will be selected for study (500 smokers and 200 nonsmokers). Lung cancer cases will be identified from a population-based cancer registry by means of a rapid ascertainment system. Cases will include women between the ages of 30-84 years who have lived in the area for at least one year prior to cancer diagnosis.

Women between the age of 30 and 84 years who have lived in the area for at least one year will be eligible to serve as controls. Potential controls for cases 30 to 65 years old will be identified by randomly selecting names from a sampling frame constructed from computer tapes listing the names of state residents obtained from the bureaus of motor vehicles or other sources.

After a random sample is selected, the names will be frequency matched to the age profile of female lung cancer cases from the State Cancer Registry for an earlier year. If the women have a diagnosis of lung cancer, they will be excluded. Controls also will be matched to cases on smoking status to insure statistical efficiency and controlling for confounding by a randomized recruitment technique.

Once an eligible case has been identified, permission to enroll the case in the study will be sought from the personal physician. When the physician's permission has been granted, a case contact letter will be typed and mailed. Seven days after the mailing date, the case will be called to obtain permission and a telephone interview will be scheduled. If convenient, the brief telephone interview will take place immediately after permission is granted and an appointment will be made for the longer (75

minutes) in-person interview.

With regard to cases who have died, the closest available relative who has been living in the same household during the cases' adult life will be contacted. The spouse, sibling, child (adult), or parent will be requested for interview and the interview will be conducted with the individual most familiar with the case. The next-of-kin's name and address will be requested from the physician when telephoned for permission.

The portion of the questionnaire dealing with diet will be a modified version of the 100 item food-frequency questionnaire developed by Dr. Gladys Block. The portion of the questionnaire dealing with diet will be a modified version of the 100 item food-frequency questionnaire developed by Dr. Gladys Block (Block et al., 1986). The food list and the nutrient values included in this questionnaire were developed using dietary data from adult respondents to the Second National Health and Nutrition Examination Survey (NHANES II). The standard questionnaire will be modified to provide better estimates of dietary fat and to enable placing individuals into categories of HAA exposure based on cooking practices. The dietary methodology to be used in this study will include a detailed questionnaire administered by a trained interviewer rather than self-administered. This questionnaire worked well in the field and is designed to obtain a complete history of residence, personal health, family health (first degree relatives), occupation, passive and active smoking.

An attempt will be made to place two radon monitors (alpha track etch detectors) in the current home of each case and control for one year. One detector will be placed in the bedroom and the other detector will be placed in the room identified (by the case or control) as the place where they spend the greatest portion of their waking hours. With the cooperation of the homeowner, our interviewer will ensure that the detectors are correctly placed so that they accurately measure the average radon concentration at the location of the monitor during the monitoring period. In addition, we will also place CR-39 detectors on appropriate glass (e.g., glass mirror, glass picture frame) items found in the current home of each study subject. CR-39 detectors are 2 inch by 2 inch plastic sheets that are etched by the alpha radiation of radon progeny trapped in the glass object. In a recent study (Mahaffey et al., 1992) the tracks left on the CR-39 detectors were shown to give a 30-year cumulative measure of radon exposure comparable to the cumulative measure given by standard track-etch detectors taken in each home occupied by the subject for the past 30 years. In conjunction with a standard track-etch measurement in the latest home of the study subject, CR-39 radon dosimetry is generally superior to other dosimetry strategies. It has been found that 30% of previous homes occupied by women in our ongoing radon study were unavailable for traditional dosimetry measurements (i.e., out of state, home demolished or current occupant refused admittance). The absence of exposure information is a serious limitation of practically all radon studies, but does not affect CR-39 dosimetry which does not require actual measurements to be taken in previously occupied homes. Using CR-39 dosimetry, we expect to have complete 30 year dosimetry for at least 90% of the study subjects. This will greatly enhance our ability to detect a correlation between indoor radon and lung cancer if such an association exists.

Field representatives will check pathology laboratory reports monthly, or more frequently if necessary, at all hospitals in the state selected for study. At some hospitals, pathology laboratory staff or medical records department staff will routinely check for patients monthly to determine whether or not there are any cases. For hospitals not following the above procedures, the field representative will check pathology laboratory reports personally and will complete the case ascertainment sheet at the hospital.

Odds ratios for a variety of exposures will be calculated by methods currently being developed for the randomized recruitment technique. In addition, multivariable logistic analysis will be pursued to control simultaneously for a variety of factors.

The histologic types of all lung cancer cases will be confirmed by a panel of three respiratory pathologists. Three two-day review meetings will be necessary.

The board also unanimously approved: a noncompetitive five-year contract for $6.25 million to the Univ. of the West Indies and the Caribbean Epidemiology Center to continue studies under the contract titled "Epidemiology of Human T-cell Leukemia/Lymphoma Virus and HIV in the Caribbean;" $100,000 for a four-year interagency agreement with the Centers for Disease Control for "A Study of Human Health Consequences of Polybrominated Biphenyls Contamination of Farms in Michigan;" $50,000 for a noncompetitive contract to the National Academy of Sciences for "Comparative Toxicity of Naturally Occurring Carcinogens;" and expenditure of $175,000 in previously obligated funds to the Environmental Protection Agency for "Dose Response Relationship at Low Carcinogen Concentrations in a Small Fish Carcinogenesis Model."

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD.

RFP NCI-CP-21003-36

Title: Provide animal facilities and conduct experiments and tests
Deadline: Approximately July 23

NCI is soliciting proposals for providing animal facilities and conducting experiments and tests. A five year award is estimated. Animals will include nonhuman primates, mice (SCID and nude), rats, goats, and hamsters. An offeror must meet a mandatory qualification criterion which requires that the offeror must 1) have animal facilities and standard operating procedures which meet biocontainment level three standards in order to conduct work with animals infected with human and nonhuman primate retroviruses (HIV-1, HIV-2, SIV, and HTLV-1), 2) have biocontainment laboratory facilities (P2 with P3 capability) to conduct work in vitro with human and nonhuman primate viruses such as HIV, SIV and HTLV, 3) be able to deliver blood cells and other tissue from experimental animals under sterile and viable conditions to Bethesda, MD, within one hour after processing, 4) have an approved Animal Welfare Assurance on file with the Office of Protection from Research Risks. The incumbent contractor is Advanced BioScience Laboratories Inc.

Contract Officer: Patricia Rainey
RCB Executive Plaza South Rm 620
301/496-8611

NCI Contract Awards

Title: Cancer following long term exposure to radioactive thorotrast
Contractor: Danish Cancer Registry, $115,191; and Presidents and Fellows of Harvard College, $648,566.

Title: Tracing for former firefighters through credit bureau records.
Contractor: Equifax Government & Special Systems Inc., $12,321.