THE CANCER LETTER

Vol. 7 No. 46

Nov. 13, 1981

Subscription $125.00 per year

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DCBD BOARD APPROVES CONCEPTS FOR $3.5 MILLION IN NEW GRANTS, $1.9 MILLION IN CONTRACT SUPPORTED PROJECTS

The NCI Div. of Cancer Biology & Diagnosis Board of Scientific Counselors has approved the concepts for $3.5 million in new projects to be supported by grants and $1.9 million in new projects to be supported by contracts, plus a $300,000 current support contract which will be recompeted next year. The grant money will be earmarked through the RFA (request for grant application) mechanism, with funding anticipated for the 1983 fiscal year. *(Continued to page 2)*

In Brief

SENATE COMMITTEE REFUSES TO CUT NCI 1982 FUNDS; LINUS PAULING TO SPEAK AT CONFERENCE ON VITAMINS

SENATE APPROPRIATIONS Committee approved the Labor-HHS Subcommittee's recommendation of $1.034 billion for NCI in the 1982 fiscal year, alleviating somewhat the fear of a massive 12 percent cut in the Cancer Program budget. Not only did the final markup not chop 12 percent from the Administration's original request of $1.026 billion, but the extra money (about $8 million) voted by the subcommittee was left intact. If the full Senate agrees when the bill reaches the floor (it had not by press time), the conference with the House will not have much of a difference to negotiate. The House voted $1.030 billion for NCI. Some reduction from the amount finally adopted by Congress still could be made through a rescision but that would require concurrence of both houses. . . . **HHS SECRETARY** Richard Schweiker has signed the order making the National Toxicology Program permanent. Until he did so, a Carter Administration recommendation that NTP be taken out of temporary status had lain dormant. . . . **RENILDA HILKEMEYER**, director of nursing at M.D. Anderson from 1955 to 1979, has received two recent honors—the new child care center for employees of all hospitals in the Texas Medical Center has been named the Renilda Hilkemeyer Child Care Center in recognition of her efforts to secure adequate facilities for nurses with small children; and she received the American Cancer Society's Distinguished Service Award for her work in oncology nursing. She has served on NCI advisory groups, as a member of the cancer control education, intervention program, and grant review committees. . . . **LINUS PAULING**, who for years has pressed for research on vitamin C in both the prevention and treatment of cancer, heads a list of speakers lined up for the First International Conference on Modulation and Mediation of Cancer by Vitamins in Tucson Feb. 23-26. The conference will concentrate on vitamin A and the retinoids and vitamins C and E. Symposia are scheduled on general mechanisms, carcinogenesis, biological modification of tumor cells, and clinical studies. Contact Mary Humphrey, Univ. of Arizona Cancer Center, Tucson 85724, phone 602-626-6044.

BOARD REJECTS MONOCLONAL ANTIBODY STUDY, BREAST TISSUE REPOSITORY

(Continued from page 1)

Until last year, the Board has only seen and discussed the intramural side of the division, leaving the extramural aspects to the Breast Cancer Task Force and Diagnostic Research Advisory Group. The Board appeared uncomfortable with a number of the extramural projects, particularly in the Breast Cancer Program.

One new project titled "Markers for Breast Cancer: Clinical Development and Testing of Monoclonal Antibodies," which was to have been supported through grants, was disapproved. Board Chairman David Korn said that "NIH already supports a lot of monoclonal antibody work. Collaboration is such that we don't need to stimulate (the field)."

Another, proposed as a contract, titled "Repository for Breast Cancer Tissue," was also disapproved. Board members at first thought the repository would be a resource open to all investigators, but changed their minds when they learned that it was not such a bank. Korn said, "This is not a resource. This is funding of science that should be funded legitimately (through traditional R01 applications)."

The Board deferred a project designed for contract support, "Preparation of Antibodies Directed Against Steroid Hormone Receptors," which had a $175,000 first year cost projection. Consultant Thomas London suggested that, rather than NCI establish its own resource for the materials, it "spread $175,000 around" and let investigators buy them from commercial sources. Korn commented that "as soon as you advertise (the availability of a free resource) people want it."

Breast Cancer Program Coordinating Branch grants approved in concept and which will be developed into RFAs were:

Epidemiology of Breast Cancer in Underexplored Special Ethnic Subsets of the Population. Two or three awards, estimated total cost of $400,000 in the first year, $450,000 in the second, and $500,000 in the third. Staff narrative:

Purpose is to call for studies to explore the risk factors for breast cancer in ethnic subsets of the population that have not been adequately studied.

International comparisons, as well as studies on migrant groups and ethnic subsets of the population, have revealed marked differences in breast cancer incidence among different racial and ethnic groups. Epidemiological attention addressing these comparisons have emphasized, for example, Eastern (Asian) vs. Western (Caucasian) differences and have focussed largely on general dietary and/or reproductive patterns. Certain important subsets of the U.S. population still remain underexplored, e.g., Blacks, Hispanics, American Indians, and Eskimos. Some of these groups appear to be at decreased risk for breast cancer, but we know little about whether or not the risk factors for breast cancer, and the natural history and development of breast cancer, in these groups are identical with those observed for the more extensively studied ethnic groups, such as Caucasians. The essential questions are (1) how much universality is there across ethnic groups for known risk factors for breast cancer, and (2) are there other, new risk factors for breast cancer in underexplored ethnic subsets of the population. The RFA would call for studies addressing underexplored racial and ethnic groups, specifically, and examining their breast cancer epidemiology, etiology, and pathologic spectrum in greater breadth as well as detail.

Luteal Phase Defects and Breast Cancer Risk. Two awards, estimated total cost of $450,000 for the first year, $500,000 for the second, $560,000 for the third. The narrative:

Purpose is to encourage research that would investigate the possible role of luteal phase defects, and particularly progesterone deficiency, on subsequent development of breast cancer.

The "estrogen window" hyposthesis postulates that breast cancer risk may be related to hormonal profiles that result in prolonged estrogen impact on target breast tissue unopposed by protective progesterone, as in prolonged periods of anovulatory cycles around the time of menarche, perimenopausally, or throughout the reproductive years in women who exhibit infertility due to progesterone deficiency (all of these representing periods of an "open window" to estrogen impact.) Preliminary data that support this hypothesis exist, and a workshop on this subject was sponsored by the Epidemiology Section in December, 1979. Preliminary search since then indicates that cohorts probably do exist of women with a history of perimenarchal anovulation, of women with a history of infertility for some of whom progesterone deficiency may have been documented, and possibly of women with a history of prolonged menopause. Our plan is for an RFA that will call for studies that will search out and explore such cohorts, following up for the subsequent development of breast cancer and examining the possible association between such histories and breast cancer risk. Hopefully, progesterone deficiency per se will also be documented in a subset of these cohorts and thus can also be specifically examined for association with breast cancer risk.

Cytogenetic Studies of Transformed Mammary Cells and Mammary Tumors Through Chromosome or DNA Mediated Gene Transfer. Three or four awards for three years at an annual cost of $450,000, $500,000 and $550,000. The narrative:

Purpose is to encourage research on the cytogenetics of normal, potentially premalignant, and malignant mammary cells, both human and other species, using currently available methods of gene transfer.

New and developing tools in cell hybridization, microcells, DNA transfection, and related areas make such research timely and important. Studies on somatic cell hybridization and the expression of malignancy have primarily used mouse fibroblasts and tumor cells from various species; such fibroblasts seem to accept transferred genes more efficiently than do other cell lines. Studies using human cells have been handicapped by a lack of human tissue. However, a variety of human breast cancer cell lines is now available, as are primary noncancer breast epithelial cells prepared from reduction mammoplasties. The latter have a limited life span and are therefore advantageous for cytogenetic studies; if neoplasia occurs as a result of specific gene transfers, only those cells that incorporate the tumor genes should survive and replicate continuously. Elucidation of cytogenetic abnormalities associated with mammary cell transformation go hand in hand with the search for such abnormalities in human breast cancer, especially in human breast cancer that appears to have a genetic component in its etiology (i.e., tumors in breast cancer prone families, in which segregation of the disease has been followed and genetically analyzed) or breast cancer thay may have been radiation induced. One highly desirable approach

might be to examine such relevant information about the host of origin for a breast cancer cell line. Emphasis on human cells is encouraged, and access to human noncancerous mammary tissue, as from reduction mammoplasties, is important. One desirable option would be to study also such "normal" mammary cells from women who are considered to be at genetic high risk of breast cancer, and similarly to examine potentially premalignant cells prepared from "benign" breast lesions in such women. Method of introduction of the genetic material into the recipient cell(s) would be left to the discretion of the investigator. This research approach could also be a powerful tool for exploring possible phenotypic expressions of a cytogenetic abnormality, such as cell surface properties or hormone receptor production of the transformed cell.

Clonogenic Assays Predictive of Sensitivity of Human Breast Cancer to Specific Chemotherapeutic Agents. Two awards for three years at an estimated cost of $250,000 per year. The narrative:

Purpose is to encourage research in the development of techniques for growing human breast cancer cells in cultures suitable for testing sensitivity to chemotherapeutic agents. It is also desirable that the laboratory assay data be correlated with clinical results to evaluate the efficacy of the chemosensitivity testing.

The current technology for growing cell aggregates in soft agar is the most promising lead thus far. However, early reports indicate that several human tumors (e.g. ovary, melanoma) are more easily grown than breast cancers, and these test systems are receiving the most attention. The high incidence of and mortality from breast cancer warrants its being the major target in one or more research projects.

Adjuvant cytotoxic chemotherapy is more commonly used following local treatment for patients with metastases in axillary lymph nodes. As many as five drugs are included in these treatment regimens. No information is available to predict sensitivity of the individual patient's tumor. An assay that would yield such information in a reasonable length of time such as two weeks would not only assure the effectiveness of the drugs administered but also obviate the administration of clinically ineffective and potentially toxic drugs.

Reports on concept reviews by the boards of scientific counselors of NCI divisions provide readers of *The Cancer Letter* with advance notice of the institute's spending plans which will show up in RFPs and RFAs in subsequent months. Those interested in participating in programs approved by the BSCs should be aware of two points:

- **The dollar figures cited as first year or total awards for each contract program are NCI staff estimates only and should not unduly influence development of proposals. These will be competitive awards and cost is a factor in selection of successful proposals.**
- **In no event should proposals be written until requests for proposals (in the case of contracts) or requests for applications (for grants and cooperative agreements) are available. Announcement of their availability will appear in *The Cancer Letter.***

Two new projects in the Tumor Biology Program to be supported by grants received enthusiastic concept approval by the Board:

Shared Instrumentation Grants for Immunology and Tumor Biology Grantees. Estimated cost for one year, $1 million to $1.5 million, 20-30 awards.

The peer review system has not been approving certain kinds of instrumentation because of the high cost and difficulty of justifying sole use of a particular instrument for a single study. In FY 1980 and FY 1981, the National Institute of General Medical Sciences advertised RFAs for shared instrumentation that were received with considerable enthusiasm by the scientific community. High cost instruments for NMR, electron microscopy, spectroscopy, protein sequencing, amino acid analysis, mass spectroscopy, cell sorters and light and fluorescent microscopy were provided on a shared basis to NIGMS grantees.

The Cancer Biology Branch supports studies in most of the same area of basic research as NIGMS and has confirmed that many grantees supported by the Tumor Biology and Immunology Programs have had great difficulty in acquiring some of the larger, more complicated instrumentation. Thus, we are considering an RFA after the RFAs successfully employed by NIGMS.

The RFA would encourage the submission of R01 applications and would include, at a minimum, the following provisions: (1) requested equipment would have to be greater than $30,000; (2) no single award would be for greater than $200,000; (3) the request could include one-half of the salary for a qualified technician for up to three years; (4) if the maximum amount to cover the total cost exceeds $200,000, no award would be made unless the remainder of the funding is assured; (5) a minimum of 50 percent of the grant would be to support two or more users from the Cancer Biology Branch and 25 percent of the grant could support any other NCI grantee.

The only objection Board members had to this proposal was that it should be open to all grantees of NCI. Branch Chief Brian Kimes agreed, and said he phrased the proposal in the more limited way because he thought that would be the only way he could get approval. "I feel strongly that we should get something (like this) going. Our program alone could justify the expenditure." Board consensus was that it should be opened up to all NCI grantees, if possible administratively. Division Director Alan Rabson indicated he thought it would be possible.

Kimes noted that "there are tough years coming up. It's getting difficult to get funds for experimental instrumentation. Our analysis shows that study sections are not approving (such expenditures)."

Korn was concerned that funds for instrumentation would compete with R01 funds. Rabson said that "hopefully these would compete with targeted areas—perhaps use end-of-the-year money—and not compete with R01 funds."

Cryopreservation of Morris Hepatomas. Two awards for two years, estimated first year cost, $100,000.

More than 35 hepatocellular carcinomas, transplantable in rats, have been developed and characterized over the past 25 years by Harold Morris at Howard Univ. They exhibit different growth rates, chromosome number, pathological degrees of differentiation, isoenzymes, regulatory molecules, and certain special characteristics. NCI supported this project as an R01 grant for 14 years, terminating last June 30. On July 1, 1981, NCI awarded a contract to Howard Univ. with Wayne Criss as principle investigator, to maintain 11 of the hepatomas and to supply them on request to scientists for research purposes. The concept for the RFP was approved by

the Board of Scientific Counselors of DCBD in September, 1980. One component which was eliminated from the RFP by the Board intended to "provide the technical and professional staff required to develop procedures for freezing Morris hepatomas without losing viability or properties characteristic of each tumor type." The Board said, "We do not believe, however, that the contract mechanism should support the proposed research and development in cryopreservation." The necessity for assessing the feasibility of preserving these 11 hepatomas by freezing procedures was emphasized again during review of the contract proposal. According to the catalogue, one fast growing Morris hepatoma (5123) has been successfully cyropreserved at the Mason Research Institute. Whether or not the characteristic biological properties have been successfully maintained is not known. Hepatomas characterized by slow growth have apparently not been subjected to cyropreservation.

The proposed project would (1) develop procedures for successful freezing of two fast growing and two slow growing Morris hepatomas to be used as prototypes, (2) develop a panel of assays that would demonstrate the persistence of important biological characteristics after recovery from freezing and transplantation once again into live rats.

New grant supported projects in the Diagnosis Program approved for announcement as RFAs:

Immunohistochemical Classification of Solid Tumors. Three grants, first year total cost of $300,000, second year $330,000, and third year $363,000.

This announcement would stimulate studies that attempt to enumerate a variety of definable antigens found in tumor cells. Immunohistochemical techniques are available that allow the examination of fixed tissue from previous biopsies, surgical specimens and autopsy material. Retrospective correlation with clinical features may provide indications for which immunochemical markers can aid in determining prognosis, selection of therapy, detection of early recurrent tumor, etc. The description of tumor cells by functional characteristics in addition to traditional morphologic and chemical staining patterns could lead to new classification schemes that would provide more information relative to the clinical picture.

The definition of T and B cell antigens, surface immunoglobulins, Fc and complement receptors has led to improved classification of the leukemias and lymphomas and this type of functional characterization should be extended to solid tumors. The Diagnosis Program is actively interested in tumor-associated substances as markers with several uses. Frequently serum and urine obtained at the time of initial diagnosis or before initiation of treatment are not available, whereas fixed tissue is usually a permanent feature which is available for most cancers. Therefore the analysis of fixed tissue may provide insight into which markers are baest for monitoring therapy in addition to predicting response to therapy.

Specific Immunoassays for Cancer Associated Isoenzymes. Three grants, first year total cost of $300,000, second year $330,000, and $363,000 third year.

This RFA would stimulate the development of monoclonal antibodies to various isoenzymes that have been shown to be quantitatively increased in certain cancers. A large number of enzymes has been lined with human cancer using cumbersome and relatively crude biochemical techniques. Consequently, there are many inconsistencies in the data. Some of these may be due to variations in the subspecificities and cross-reactivities of the antibodies, problems in detecting low but still abnormal levels in the serum by classical electrophoretic and staining techniques, and the inability to distinguish many isoenzymes by classical immunology. The objective would be to develop sensitive quantitative assays using monoclonal antibodies which could with more sensitivity and accuracy measure isozymes in the serum for their more effective utilization as diagnostic aids for cancer.

There is a need for developing antibodies that recognize isozymes with great specificity and are not dependent upon functional activity or physicochemical properties of the enzyme for that specificity. The development of monoclonal antibodies provides the technology for the production of such antisera with the built-in ability to insure reproducibility of results for unlimited numbers of tests. This technique is being widely used for detection of tumor related surface antigens. However, little is being done to exploit its potential use in localization and quantitation of cancer associated isoenzymes.

Non-Invasive Approach for Detection of Lung Cancer. Two grants, estimated first year cost of $300,000, second year $330,000, third year $363,000.

This RFA would encourage pilot studies involving the use of gas chromatographic-mass spectrometric techniques for the chemical analysis of volatile organic components of human expired air in an attempt to isolate, identify and quantify lung cancer characteristic and/or associated constituents which may have potential for early diagnosis. Profiles of patterns from lung cancer patients would be distinguished from those of patients with carcinoma in situ, pneumonia, and a variety of other associated diseases including chronic bronchitis, bronchiectasis and emphysema.

The technology is available and capable of automation if pilot studies should be suggestive. It could greatly reduce the psychological, logistic and economic problems frequently encountered with the present techniques and address the crucial issue of early detection.

The high mortality of lung cancer may be due to late diagnosis. Because current screening methods by sputum cytology and chest radiography do not provide convincing evidence that this dilemma can soon be resolved, newer approaches to detection must be sought. Studies in physiological chemistry show that the composition of expired air in health reflects the relative amounts of all volatile constituents in the blood, and that in disease it would include those compounds which are intimately associated with pathologic processes. Hence, volatile expired constituents offer a potential source of fundamental knowledge not only of the normal processes but may act as chemical signals for early detection and diagnosis of disease states of the body. Preliminary data are already available on normal profiles for correlation with the disease state. Other studies have documented the significance of this technique in diagnosing chemical exposure. These proposed studies would be a first step in acquiring data to assess its value in lung cancer diagnosis.

Two grants, estimated first year cost of $300,000, second year cost of $330,000 and third year cost of $363,000.

Korn cracked that "one has visions of street corner machines—go in and get your breath analyzed for cancer." He added that "it seems a novel idea. I don't know if anything will come of it, but it's worth trying."

Two contract supported projects in the Breast Cancer Program, one a new repository for human breast tissue from non-cancer patients, and the other an ongoing bank of cryopreserved animal and human tumors and human breast cancer cell lines, will be combined into one project as a result of the Board's action.

The animal and human mammary tumors bank facility, run by Mason Research Institute, was

scheduled to be recompeted when the current contract expires in June, 1982. Cost-saving was the rationale for combining the two repositories. Staff-prepared narratives for the two proposals:

A Central Repository for Human Breast Epithelium from Non-Cancer Patients. Cost estimate: one award for three years, first year $175,000.

The laboratory must have access to normal mammary tissue which is to be obtained from reduction mammoplasties since tissue obtained from surgical specimens a distance from the neoplastic tissue or even in the contralateral breast are questionable as to normalcy. At all times the specimens must be handled under sterile conditions in order to prevent contamination. The contractor will be reuqired to maintain a clinical file and histopathological report on all specimens.

Presently there is no known long term transplantable human, normal mammary cell line. Previous sources of non-cancer breast epithelium were obtained from normal, human breast aspirations, nontumor mastectomies and reduction mammoplasties. Use of benign breast tissue for experimental control studies led to concerns that these may be preneoplastic tissues.

There is an increasing number of reduction mammoplasties being performed for cosmetic reasons. The tissue is available in bulk and can be processed for preparation of organoids and single epithelial cells. These can be used as control material for experimental studies in molecular biology, biochemistry, cytogenetics, and cell transformation.

Animal and Human Mammary Tumors and Human Breast Cancer Cell Cultures. The contract is currently in its second year of three at a cost of $142,115. Cost projection for the final year is $164,615.

The project maintains a bank of cryopreserved animal and human tumors and human breast cancer cell lines including many with unique biological and endocrinological characteristics. In addition antibodies to various types of collagens and procollagens, and antigen and antibodies of human and rat alpha lactalbumin are maintained. Characterization studies are done on each tumor system prior to cryopreservation as well as on three generations post freeze and thaw. Studies include growth curves, host survival time, histopathology, organ weight changes, effects on plasma hormone levels, preservation stability, and recovery of special and unique biological characteristics are a primary concern. Monitoring for contamination (bacterial, viral, fungal) is done routinely. Historical data (published and updated) are documented on each tumor system and cell line along with transplantation methods. The information is updated each year and prepared in a catalogue. Also, a bibliography of published research on each system, tumors or cell lines, is updated yearly. These tumors and cell lines are available to scientists throughout the world upon written request and approval of the project officer at a cost for shipping.

Currently there are 233 different tumors or tumor sublines cryopreserved in 5597 ampules plus 24 different human breast cancer cell lines in 1865 ampules. In the past year 185 animal tumors have been shipped to 94 investigators; 91 different cell line shipments consisting of 326 cultures went to 60 different laboratories. Since the human and rat alpha lactalbumin and antibodies became available a total of 17 requests has been received. Five of these were for both human and rat antigen and antibody. Three requests were received for the rat antibody only. The antibodies to the various collagens and procollagens have not been shipped to date. These will be available to investigators within two months. From 1968 to the present 245 scientific papers published in refereed journals have acknoweldged receipt of tumor systems or cell lines from the bank.

Other new contract supported projects in the Breast Cancer Program given concept approval were:

Evaluation of Diaphanography for the Diagnosis of Breast Cancer. Two awards for five years, totalling $300,000 for the first year. Subsequent costs would be $375,000 for each of the second, third and fourth years, and $300,000 for the final year.

Diaphanography or transillumination is a noninvasive diagnostic modality that uses intense light rays to illuminate the tissues of the breast. The light can be used to visualize the internal structures directly or to produce images on film or videotape. Diaphanography as a diagnostic modality for breast cancer has recently been introduced into the United States by several European companies. FDA has approved these instruments for sale and many firms are now planning to market their equipment.

This modality needs scientific evaluation to determine its capabilities and limitations and to compare its advantages with other modalities. Scientific evaluation is essential since a considerable amount of publicity has now been given to the merits of diaphanography including the lack of irradiation. There are no clinical trials in progress.

The clinical evaluation of new diagnostic modalities for breast cancer has traditionally formed an integral part in the overall objectives of the Breast Cancer Task Force. Because this study will require careful coordination and program involvement, the contract mechanism is necessary.

Breast Cancer Program Coordinating Branch Chief D. Jane Taylor said NCI "has had a lot of questions from women about this. It's been written up in magazines." She added that FDA user approval does not mean the procedure has been tested for effectiveness.

Consultant Kenneth Olden asked if there was any information from industry. "No, that's what is surprising," Taylor responded.

Diagnostic Projects Section Chief Donald Henson said the technique goes back to the 1920s, using a flashlight, but if there were enough light, it got too hot. The idea was picked up in the 1970s when cold light came in.

Development of New Diagnostic Modalities for Breast Cancer and Clinical Feasibility Testing. One award, four years, estimated cost $200,000 the first year, $200,000 the second year and $225,000 each for third and fourth years.

Purpose of the project is to support the development of NMR imaging for breast cancer and other breast diseases.

Mammography is a proven technique for the diagnosis of breast cancer with a remarkable record of success. However, because of the risk associated with x-ray exposure, it cannot be used as a surveillance technique in women under the age of 50 and the possibility of inducing cancer, even in a small percentage of patients, is a legitimate concern. The alternatives are diagnostic ultrasound and thermography, which, in spite of intensive study, have not as yet proven themselves. Furthermore, x-ray mammography is practically useless in the dense or fibrotic breast. New imaging procedures may not only complement x-ray mammography, but may prove superior in the detection and diagnosis of breast cancer. For instance, computed tomography scanning and heavy ion imaging utilize ionizing radiation in forms specially deisgned to provide precise determination of tissue density, permitting detection of breast cancer by virtue of a demonstrably higher density than benign lesions.

Nuclear magnetic resonance imaging is an untried method for breast cancer diagnosis, but if offers special promise because it does not use ionizing radiation and is nonhazardous.

NMR imaging is a noninvasive technique that utilizes the interaction between magnetism and radiowaves to portray tissue structure. There is potentially more contrast in an NMR image than in its x-ray equivalent. NMR is approaching clinical application. Preliminary clinical trials are under way in other anatomic sites. These trials include both imaging and scanning and we believe the breast should also be included.

Determine if Reflectance Spectroscopy Can Be Used to Diagnose Breast Cancer. A Feasibility Study. One award, $200,000 the first year, $225,000 the second, $250,000 the third year and $200,000 the fourth year.

Purpose is to determine the feasibility of using reflectance spectroscopy to localize lesions in the breast and what other information it can provide about the internal structure of the mammary gland.

Reflectance spectroscopy is a novel analytical technique that is used by the U.S. Dept. of Agriculture to measure the internal composition of potatoes, tomatoes, applies, and other large fruits and vegetables. A form of transillumination, the procedure measures the light that is reflected by a substance, not the absorbance of transmission.

By varying the wavelength and geometry of the incident light, considerable information about the internal structure of a body can be obtained by measuring the second derivative of the reflected light. The light can also be used to develop an image or produce a videotape. The technique has not been adapted to diagnostic medicine, although ophthalmologists are beginning to use it to determine the composition of cataracts. It seems ideally suited for the breast.

Provide Serum and Tissue Specimens to Scientists Searching for New Tumor Markers. This is a small project designed to facilitate the development and use of monoclonal antibodies in breast cancer, estimated at $75,000 per year.

Purpose is to make available to basic scientists breast cancer tissue and serum specimens for their research.

Obtaining tissue and serum to conduct basic type research or to develop new tests can be difficult for a bench scientist. Although a serum bank is available in breast cancer, the bank only provides serum in small amounts to investigators who want to perform a blind study on a test already developed. The serum cannot be used to develop a new test or for investigators to use in their experiments. Many investigators working with monoclonals expressed difficulty in obtaining material from breast cancer patients for research. We propose to simply arrange for the collection of human material when needed by investigators.

Three new contract supported projects asked by the Diagnosis Branch were given concept approval despite concern by Board members that there was already a great deal of work going on in those areas. Of one on evaluation of CEA for monitoring colorectal cancer therapy, consultant Howard Sussman commented that "this might be the last study needed" on the subject.

Evaluation of CEA for Monitoring Colorectal Cancer Therapy. One award, approximately $250,000 first year. The clinical study will require two years for recruitment of patients who will then be followed for five years. Cost of subsequent years would be $275,000 second year, $300,000 third year, $330,000 fourth year, $360,000 fifth year, $330,000 sixth year, $300,000 seventh year.

Through the Gastrointestinal Tumor Study Group NCI supports treatment protocols for the evaluation of adjuvant therapy for patients with surgically resected carcinoma of the colon. In addition GITSG has been interested in evaluating CEA as a prognostic and monitoring adjunct to patient management. Various cooperative treatment groups also have ongoing randomized trials for therapy of colon cancer. The clinical studies with patients are available for the evaluation of CEA through existing protocol studies and would not produce additional expense beyond those connected with the CEA assay.

This project would provide a central facility for performing the carcinoembryonic antigen assay for a number of different investigational groups involved in a cooperative clinical trial aimed at improving the monitoring of patients with colorectal cancer. In addition to the CEA assay, this facility would serve as a central reference point for the study to store the serum samples, keep uniform data on patients in the study, provide logistical support for serum shipments and return of assay results. The single laboratory for a cooperative study would simplify quality control and comparability of assay results and would facilitate the comparison of the participating groups.

It has been shown by several groups that resection of recurrent colorectal cancer in selected patients can sometimes lead to cure. The earlier the recurrence can be diagnosed, the more likely is treatment to be beneficial. It has also been demonstrated that monitoring of serum CEA is the most effective way, along with clinical history and physical examination, to detect recurrent tumor. Evaluation of CEA monitoring in colorectal cancer has not yet been achieved because of the lack of a controlled prospective study. The major impediment to such a controlled study has been the absence of an appropriate central laboratory for insuring comparability of CEA assay results among the participating clinical centers.

Establishment of an excellent CEA laboratory capable of participating in a clinical trial will not only provide an answer for the value of CEA in the management of colorectal cancer, but will also serve as a model for the evaluation of CEA in other malignancies such as lung and breast cancer and provide a model for the use and evaluation of other tumor markers.

Nucleosides and Bases in Diagnosis of Cancer. Two awards, three years, $250,000 first year, $275,000 second year, and $305,000 third year.

Primary objective is to assess the diagnostic and prognostic potential of altered nucleoside and base patterns is serum and/or urine of patients as biological markers of malignancy using high performance liquid chromatography. Profile comparisons would be made between patients with cancer, patients with corresponding benign diseases and healthy controls. Correlations will be made with stage of disease and experimental and clinical parameters. Another objective would be to gain an understanding of the causes and/or effects of altered nucleoside and base patterns and how they relate to the presence of neoplasms.

A special requirement would be access to advanced analytic technology to determine simultaneous and quantitative measurements of compounds in different metabolic systems with high sensitivity and resolution. Any laboratory having the expertise and availability of such equipment would be eligible.

There has been some work on the potential value of serum and urine nucleosides and bases and biologic markers for early detection of cancer. The rationale for this is based on the knowledge that malignant cells have altered rates of cell division as evidenced by their uncontrolled growth as well as altered rates of nucleic acid biosynthesis and catabolism. Thus, abnormalities in concentrations of these substances as a result of the neoplastic process should be reflected in urine and blood. The recent development of new analytical methodology i.e., reversed-phase high performance liquid chromatography has greatly expanded efforts in a broad range of biomedical research. Thus far, contributions to the diagnosis or prognosis of cancer have not been fully explored.

In studies with blood, it has been reported that there are

elevated concentrations of pseudourine, and N^2, N^2-dimethylguanosine in the sera of patients with acute leukemia and breast cancer. Furthermore, elevated levels of 1-methylinosine and N^2-methylguanosine have been found in the sera of some patients with histologically documented breast cancer, while patients with benign fibrocystic disease showed no elevations. Several nucleosides and bases, which are important in purine metabolism have been found to be increased in plasma of patients with acute lymphocytic leukemia.

More work has been done on the assessment of concentrations of modified nucleosides in urine and their value in diagnosis. For some time it has been known that cancer patients excrete certain methylated purines and other products in elevated levels in their urine. Studies have shown that the specific breakdown of †RNA in tumor tissue is extraordinarily high which accounts for the very high elevations of the methylated bases in the urine of cancer patients. From these initial studies it appears that changes in free nucleoside and base concentrations in blood and/or urine may be promising for use as biochemical markers.

Use of Multiple Markers in Lung Cancer Diagnosis. Three contracts, estimated cost total $450,000 first year, $495,000 second year, and $545,000 third year.

This RFP would seek laboratories with technical capability to perform two or more assays for circulating markers associated with human lung cancer. Responders should have access to their own clinical population with oat cell and non-oat cell lung cancers with a broad range of tumor burdens, as well as nonmalignant diseases and appropriate controls. The aim of this study would be to have a battery of marker measurements performed on aliquots of blood from the same patient to determine by appropriate statistical techniques if a combination of markers providing aprofile of abnormal change might increase the specificity of the tests to the point of clinical utility. Potential offerors would need to have previous experience and available facilities to perform the proposed assays, supportive data to justify their inclusion in a lung cancer marker panel, and an appropriate clinical population.

Tumor markers, in preliminary data, have suggested they may be useful aids to differential diagnosis of cancer in individuals with signs and symptoms suggestive of cancer. Markers have been found to be useful in staging of tumors and in the assessment of prognosis in cancer patients. Serial assays of tumor markers are being performed to detect the early recurrence of cancer after tumor resection and to monitor tumor response to chemotherapeutic agents. However, the accumulated experience of many investigators has been that it may be unrealistic to expect that a single tumor marker can be found which is truly effective in clinical application for detection, diagnosis, prognosis, tumor localization and staging and monitoring of disease. Nor is it generally believed that a marker need be absolutely tumor specific to be useful. There are preliminary data suggesting that several of the knwon assays for markers, when applied simultaneously may overcome some of the problems of nonspecificity of single markers. There is an urgent need for such studies to validate these preliminary data.

To be recompeted next year when the current contract with Cor Bel Laboratories ends is a $300,000-a-year holding facility for experimental animals used by the intramural Immunology Branch. Acting Immunology Branch Chief David Sachs, responding to a comment on the expense of keeping laboratory animals by Board member Lisa Steiner, said the cost per mouse per day is about eight cents. Sachs also noted that several investigators are contemplating projects which would require an increased number of animals to be held at the facility, and suggested that the cost of the contract would increase to $375,000 a year over the next three years. The narrative:

The subject contract is a holding facility for experimental animals in support of the research efforts of the entire Immunology Branch. Each senior investigator is in full control of his/her own animals at the site, and this facility really represents eight semi-independent holding colonies supporting the research programs of each of these eight laboratories.

The contractor maintains a colony consisting of approximately 10,000 mice, 200 rats and 20 rabbits. Breedings of certain strains of mice and rats for experimental needs of individual investigators are performed when such animals are not available commercially. Limited technical support including bleedings and injections of experimental animals, passage of cell lines and collection of ascites, and palpation of mice for the detection of tumors is also provided. Subsequent to the outbreak of ectromelia at NIH in 1979, animal transfer between Cor Bel and NIH has been only in one direction, with animals from NIH not being permitted to be returned to Cor Bel. These steps were taken to assure that future disease outbreaks at NIH would not be transferred to the Cor Bel facility, at which prevention and monitoring are possible at a higher caliber than on campus. For this reason, performance of technical support at the facility has become of greater importance since this time. Animals are only transferred to NIH for terminal portions of experiments or for acute needs of animals or animal tissues.

HAWKINS PERSISTS IN ATTACK ON NCI DESPITE TESTIMONY REFUTING CHARGES

Selectivity.

If there is one word which describes the spate of criticism hurled at NCI during the siege of congressional hearings and the discredited *Washington Post* and "20/20" productions, it is selectivity, in the use of information and misinformation by the inquisitors.

Charles Young, chief of the Developmental Chemotherapy Service at Memorial Sloan-Kettering Cancer Center, used the word selective to describe material presented in the Post series. Young, testifying at one of two hearings held last week by Sen. Paula Hawkins (R.-Fla.), said Post reporters Jonathan Neumann and Ted Gup "made selective use of information given to them."

Young said that one of his MSK colleagues, discussing the investigational drug methylGAG with reporters, had told them of its effectiveness in early trials and that it is turning out to be a "very useful drug in treating lymphoma. But only negative information on the drug was used in their story."

Young, Emil Frei of Sidney Farber Cancer Center, John Durant of Univ. of Alabama Comprehensive Cancer Center, John Speer of Penrose Cancer Hospital, and Charles LeMaistre of Univ. of Texas/M.D. Anderson Hospital all presented clear, rational statements on the Drug Development Program which effectively answered most of the criticism hurled at the program by the Post and a few midlevel FDA officials. HHS Asst. Secretary for Health Edward Brandt Jr., FDA Commissioner Arthur Hayes, NCI Director

Vincent DeVita and other NCI executives presented information on various aspects of the controversy which went unchallenged.

Yet Hawkins, apparently determined to discredit NCI and its leadership, ignored almost every point made by NCI's defenders. Her opening statement at the Nov. 6 hearing offers some examples of selectivity.

NCI's Drug Development Program "is needed and must be continued, but with proper leadership," Hawkins said. "The purpose of these hearings is to rid the National Cancer Institute and its regulator, the FDA, of some very serious program deficiencies. . . . Testimony on Tuesday convinced me that NCI does not adequately protect patient safety. Management deficiencies that for years have crippled the programs of NCI and its regulator, the FDA, must be immediately eliminated. The testimony I heard Tuesday, and every hearing we hold on this subject, is evidence to the world of the critical need for better management of the National Cancer Institute."

What was this testimony?

"Although toxicity data from animal studies conducted in the early 1970s warned of the potential for methyl CCNU to cause kidney damage, clinicians were not advised," Hawkins charged.

DeVita and others pointed out at the earlier Hawkins hearing last spring, and many times since, that physicians doing the phase 1 studies for MeCCNU certainly were told of the animal kidney damage, and they watched their patients closely for that and other toxicities. No renal toxicity was observed in any of the phase 1 or phase 2 studies. Since animals are not reliable predictors of organ toxicity, and since early human trials showed no signs of kidney damage, there was no reason to warn of the possibility. Not until the drug had been in widespread use for several years did its cumulative renal toxicity become known. Hawkins chose to ignore that information.

"When NCI did learn of this drug's life threatening effects in humans, NCI did not promptly inform FDA and all of its clinical investigators," Hawkins said.

That charge also has been kicking around for months and has been explained repeatedly. NCI had never immediately passed on to FDA or clinical investigators adverse reaction reports until they had been checked out and proven correct, unless the initial evidence was convincing. In the case of the first MeCCNU report, the evidence was anything but convincing. The patient had been heavily treated with other drugs and modalities, and had not received MeCCNU for nearly two years.

When reports from other studies of renal toxicity came in and were substantiated, NCI did make the proper notifications. Hawkins ignored that point.

Some FDA officials believed that the "Memo of Understanding" negotiated between NCI and FDA about three years ago committed NCI to report adverse reactions immediately. That was not NCI's interpretation, but DeVita agreed—after the MeCCNU problem—to do so henceforth despite the certainty that many reports will be false alarms. "It will be better to err on the side of reporting a potential reaction," he said at last week's hearing.

The Memo of Understanding which has provided a basis for a smooth working relationship between the two agencies; the Master File of investigational drugs which NCI maintains for FDA; the Group A, B and C drug distribution system; and the regular meetings between NCI and FDA Bureau of Drugs senior staff all demonstrate the degree of cooperation between the two agencies. Differences of opinion, particularly those involving scientific matters, are inevitable and will continue to occur.

Hawkins, however, elected to go with the complaints of a few midlevel FDA officials rather than believe the statements of FDA senior staff. Another flagrant example is the issue of the toxicology protocol.

FDA medical officer Robert S.K. Young and pharmacologist David Richman have objected to the new protocol which calls for preclinical toxicity tests in one species, the mouse. The protocol was developed after long and serious consideration by NCI and FDA scientists and by nongovernment scientific advisors to both agencies. DeVita told Hawkins that he had counted 176 scientists who had participated in drawing up and approving the new protocol and mentioned that this was disputed by only three or four individuals at FDA. The protocol has been approved at every level of FDA, including Hayes, who considered and rejected a "citizens' petition" filed by Young.

Yet Hawkins listed among the alleged NCI management deficiencies the statement by Richman that "NCI's new and abbreviated animal testing of drugs is unsound and he is severely distressed by the necessity of having to implement it."

Hawkins relied on statements by Young, FDA investigator Michael Hensley, and FDA field inspector Laurie Meade to indict NCI for supposed deficiencies ranging from "failure to warn doctors of the life threatening cardiotoxicity of the drug DHAD" to "disorganized files." She ignored DeVita's contention that investigators had been warned to look for cardiotoxicity, that the animal studies cited by Hensley in his accusation were highly suspect, and that most of the incidents of heart damage had been traced to previous treatment or pre-existing heart conditions.

One of the animal studies had sat on an NCI staff member's desk for a week or so before it was acted upon. DeVita told Hawkins that that was "unacceptable" and, pointedly, that person was no longer with NCI.

Richman, in a statement prepared for the hearing record, criticized ***The Cancer Letter*** for its report on

the Post series. Richman agreed that the series, "albeit well intentioned, sensationalized problems of cancer chemotherapy in a manner which may have left many people with the wrong impression, that all chemotherapeutic drugs are poisons and that none are effective. That type of journalism, unfortunately, can send potentially curable cancer patients into the hands of charlatans and quacks." He continued:

It should be noted that not all misdirected sensationalism is directed at the National Cancer Institute by its detractors. Over the years verbal and printed stones have been cast against the FDA's regulation of the drug development program. Often they have been hurled by unquestioning supporters of the Institute in the same sensationalistic manner that they feel is unfair when directed against the Institute. As a recent example I cite the Oct. 23, 1981 issue of *The Cancer Letter* which deplores the lurid style of the "War on Cancer" series and decries the seemingly personal attack in it on Dr. DeVita—both observations not without some merit. *The Cancer Letter* then summarily ridicules an FDA medical officer and states as apparent fact that "All NCI has asked of FDA is that prospective anticancer drugs not be considered in the same category as new headache pills. Because so many cancer patients will die without some new therapy, NCI staff and cancer investigators feel it is not logical to demand as many safeguards as would be required for a new medicine designed to treat non-life threatening ailments." This statement seems to crop up with regularity. Often accompanying it is a specific point of fiction such as that the FDA requires two years of dosing animals with a new anticancer drug before allowing it to be given to the first cancer patient.

It might be of interest to learn just who leaks these monumental misconceptions and as to why they are published and perpetuated without being checked for factuality.

(Ed. note: Clinical investigators who have suffered through interminable delays waiting for FDA approval of INDs could enlighten Richman on that point.)

Additional comments from the Hawkins hearing will appear next week in ***The Cancer Letter.***

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

SOURCES SOUGHT

RFP NIH-NIAID-IAIDP-SS-82-2507

Title: *Maintenance of an international bone marrow transplant registry*

Deadline for submission of statement of qualifications: *Dec. 15*

The National Institute of Allergy & Infectious Diseases proposes to contract with an independent organization to maintain an international bone marrow registry whose objectives will be: 1. To maintain a statistical center for the collection, organization and analysis of clinical data provided by bone marrow transplant teams throughout the world. 2. To disseminate the results of clinically relevant analyses of pooled registry data to bone marrow transplant teams and to the medical profession for the earliest possible benefit to patients who might be helped by bone marrow transplantation treatment. 3. To aid in designing, organizing and providing statistical support for controlled, cooperative clinical trials utilizing bone marrow transplantation. 4. To assemble a listing of potential donors of bone marrow for allogeneic transplantation, the listing to include HLA typing data.

Organizations that feel they possess the necessary capabilities to perform the tasks specified above must supply the following required information: 1. Evidence of staff qualifications and experience in the areas of immunogenetics, bone marrow transplantation, oncology, hematology, and large scale data management and analysis. 2. Evidence of experience in establishing and maintaining collaboration with bone marrow transplant centers worldwide for the purpose of acquisition of clinical data. 3. Evidence of capability to acquire, maintain and disseminate data on potential bone marrow donors, for the purpose of establishing an "organ sharing network." 4. Evidence of experience in the analysis of clinical data assembled in large scale studies and in the preparation of publications presenting such data.

Concise responses addressing the above requirements are requested. Respondents should indicate their facilities and staff available to carry out the work specified, and should summarize their experience in such or similar activities. Ten copies of the resume of experience and capabilities must be submitted.

John Hamill, Contracting Officer
Contract Management Branch, NIAID, NIH
Westwood Bldg. Rm. 707
Bethesda, Md. 20205

RFP NCI-CM-27516

Title: *Production of bulk chemicals and drugs*
Deadline: *Approximately Dec. 18*

The Pharmaceutical Resources Branch, Div. of Cancer Treatment, NCI, is seeking organizations having capabilities, resources, and facilities for the preparation of bulk chemicals and drugs. Objective of this project is the preparation by synthesis of quantities of bulk chemicals and drugs (1 gram to multikilogram) for use as potential anticancer agents. Major emphasis will be on the preparation of the desired material in multikilogram scale and will involve resynthesisis and scale-up from the chemical literature.

Methods will be available for small scale runs in many but not all instances. Process development for

scaleup will be required. The facilities must have the capacity for performing all types of chemical synthesis and must be able to demonstrate organizational experience in this area. A variety of large scale and pilot plant facilities will be required.

The minimum requirement is a well equipped operating pilot plant with a wide variety of glasslined reactors up to and including a 500 gallon glasslined reactor and the necessary supporting equipment and facilities. All products must be completely assayed as to identity and purity. Analytical-instrumental facilities for the assay and identity of the materials prepared, including in-house capabilities for IR, UV TLC, GLC and HPLC, and adequate library facilities must be available.

The principal investigator must be trained in organic or medicinal chemistry, preferably at the PhD level or equivalent, from an accredited school with extensive experience in chemical synthesis and process development. All technical personnel including the principal investigator and principal assistant must be assigned to the project a minimum of 50 percent of the time, preferably 100 percent of the time.

It is anticipated that a 3½ year contract award will be made. The first six month period will require 2½ staff years of effort and the following periods will require five staff years of effort per year. The effort will be undertaken as a single contract.

Contract Specialist: Ann Linkins
RCB, Blair Bldg. Rm. 228
301-427-8737

RFP NCI-CM-27515

Title: *Preparation of radiolabeled materials*
Deadline: *Approximately Dec. 18*

The Pharmaceutical Resources Branch of DCT is seeking organizations having capabilities, resources, and facilities for the preparation of radiolabeled materials. Objective of this project is obtaining radiolabeled compounds of high purity via synthesis, fermentation, etc., in 1 to 50 millicuries quantities. Major emphasis will be on the preparation of the desired labeled compounds via synthetic procedures and will involve a wide variety of compounds, such as heterocyclic compounds, alkaloids, folic acids, alkylating agents, nucleosides, purines, pyrimidines, nitrosoureas, etc.

Compounds required may include one or more of the following radioactive elements: carbon, tritium, deuterium, sulfur, phosphorous, iodine, nitrogen, etc., and a broad NRC or equivalent license is required. Methods will be available for "cold runs" in many but not all instances. Many of the materials may be highly toxic and potentially carcinogenic, in addition to the hazard of radioactivity. Adequate containment and safety facilities must be available.

All materials must be completely characterized and assayed as to identity, purity, and radiopurity. A well instrumented analysis laboratory including a HPLC dedicated to radiosynthesis work and adequate library facilities must be available. The principal investigator must be trained in organic, medicinal, or radiochemistry, preferably at the PhD level, or equivalent in experience in radiochemical synthesis. The principal investigator must be named and all technical personnel must be assigned to the project a minimum of 50 percent of the time, preferably 100 percent of the time. The contractor must furnish all equipment necessary to safely perform the work.

It is anticipated that the project will require a total of six technical person years of effort per year. The effort will be undertaken in two contracts of three technical person years of effort each. Two individuals on each contract must devote 100 percent of their time to this project and the total project team on each contract must involve not more than four individuals.

Contracting Officer: John Palmieri
RCB, Blair Bldg. Rm. 228
301-427-8737

RFP NCI-CO-23852-41

Title: *Analytical services in support of the Div. of Extramural Activities*
Deadline: *Dec. 21*

NCI is soliciting proposals for a small business firm to provide analytical services to support the Div. of Extramural Activities Grants Administration Branch and Grants Financial Data & Analysis Branch.

This proposed procurement is a total set aside for small business concerns. Any concern bidding on a contract for services (including but not limited to services set forth in Div. I, Services of the Standard Industrial classification manual) not elsewhere defined in this section, and its average annual receipts for its preceding three fiscal years do not exceed $2 million (see FPR 1-1.701.11 for size standard differentials which are applicable to specified non-foreign areas).

This project is for a three year period. Offerors will be limited to those firms having operating facilities within a 50 mile radius of Bethesda, Md., as frequent consultation with NCI staff is often necessary.

Contract Specialist: Diane Smith
RCB, Blair Bldg. Rm. 332
301-427-8745

The Cancer Letter _Editor Jerry D. Boyd
Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.