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P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

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BIOASSAY BACKLOG REPORTS SHOW INCREASING NUMBER OF EQUIVOCAL RESULTS; IS THE PROGRAM A FAILURE?

With the reports from the NCI Carcinogenesis Bioassay Program backlog coming through in ever larger bunches, it is becoming increasingly obvious that only a few of them will definitively say either, "This chemical is a carcinogen and is a threat to humans," or "That one is not and poses no threat."

Of seven reports considered by the Clearinghouse on Carcinogens Data Evaluation/Risk Assessment Subgroup at its last meeting, defini-

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In Brief

LAWYERS HALT REFERENCE CHEMICAL DISTRIBUTION TO GRANTEES, THREATEN TO STOP VIRUSES, ANIMALS

HEW, NIH legal advisers have come up with an interpretation of the word "collaborative" that threatens to halt NCI's practice of distributing free to grantees a variety of research materials, including test animals and viruses. The legislative provisions on which such distribution has been based mentions "collaborative" researchers. For years, NCI has assumed that included grantees, but the lawyers say now that it refers only to contractors. This latest in a series of illogical legal opinions rendered by HEW was made specifically to block distribution of reference chemicals to grantees involved in carcinogenesis research. Both grantees and contractors have been receiving such chemicals, and the National Cancer Advisory Board has been trying (unsuccessfully so far) to get Congress to broaden that authority and permit distribution of reference chemicals to all scientists who can use them, whether or not they are working on an NCI grant or contract. NCI had that authority for biological agents but not for chemicals. Now, if HEW is determined to push this new interpretation to its limit, only collaborative researchers—contractors—will get the biological materials. What had been perceived as a minor flaw in the National Cancer Act has now assumed major proportions, and correction by Congress is urgently needed. A number of scientists who have been turned down in requests for materials have felt that NCI intramural researchers were responsible. That is not the case—they can lay the blame on HEW's overly strict interpretation of the law. . . . AN NIH RESEARCH team has developed an inexpensive ultrasonic "real-time" scanner for obtaining a cross section view of the upper abdomen. They say that, among other applications, the scanner can find tumors in the pancreas, liver and kidneys. The researchers are Thomas Shawker and Willard Whitehouse of the NIH Clinical Center and William Schuette of the Div. of Research Services. Unlike conventional static ultrasonic B-scanners, the real-time scanners give a continuous "fluoroscopic" image. The unit is inexpensive and can be integrated as an add on to commercially available static B-scanners, NIH said.

BETTER SCIENCE, USE OF GUIDELINES COULD IMPROVE BIOASSAY RESULTS

(Continued from page 1)

tive results were reported on only two (See following article).

"The question of carcinogenicity remains unresolved. . . Under conditions of the test, the findings are of borderline significance. . . An assessment cannot be made because of the unusual nature of the tumors. . . The results are equivocal. . . ."

Those statements have turned up with dismaying frequency in the reports—dismaying because each one refers to a test that cost from $200,000-300,000, chewed up two years of lab time and added to the burden of pathologists who had to read and interpret slides. They also placed more ammunition in the hands of the enemies of the National Cancer Program, who will say this is further evidence of NCI mismanagement.

With such a limited return on the investment of precious dollars, is it wise to continue sending more chemicals and more money into bioassay?

Some NCI executives feel that it might be better to spend the money on something else. "The Clearinghouse has a blind faith in bioassay," said one. "There's too much faith, too much optimism about bioassays. At best we can test only a few of the chemicals coming into the environment every year. Maybe we should stop testing and determine on some other basis what chemicals should be permitted."

The critics are not necessarily looking for someone to blame for the lack of results. "It would be easy to go back and say they should have done a better job of designing tests or selecting chemicals, but that wouldn't be fair," said one. "We know a lot of things now they didn't know five years ago (when most of the chemicals coming out of the bioassay went onto test)."

Clearinghouse Chairman Arnold Brown agrees and points out that a major improvement in experimental design took place about two years ago when bioassay guidelines were adopted. Chemical selection procedures also were improved. "When we start getting those reports, you'll see a big improvement in results," Brown said. "In general, the guidelines are being followed. Before, sometimes the design was good, sometimes not."

One critic suggested that customizing tests to each chemical will do more to improve results than following guidelines. "The chemical structure, pharmacologic properties and conditions of use will dictate the experimental design, rather than apply rigid guidelines," he said. Custom tests have their drawbacks—they are more expensive, more complicated, will take longer, he pointed out.

Brown says there are certain basic elements of the guidelines that pertain to all tests, elements that were not always considered in the past—requirements for minimum number of animals, size of control groups, statistical procedures, conditions under which animals were kept, and the way pathology was performed. Brown agrees that custom tests were desirable, or at least some degree of freedom should be permitted to allow variations in selection of route of administration, species, and sex.

Another improvement is that bioassay contractors are more careful, doing better work and are inspected closer, Brown said.

"The program now is running along as well as a bioassay program can be expected to," Brown said. "But bioassay is going to flunk out when it comes to weak carcinogens. Cyclamate is an example. I don't think we'll ever know if that is really a carcinogen. Bioassay just is not sensitive enough."

The Clearinghouse Experimental Design Subgroup is charged with advising the program on how to improve tests, and how each chemical should be tested. Brown feels it is providing excellent advice, based on the latest science. Neither that advice nor the science was available five years ago.

Many of the chemicals now being reported on are being referred back to the Chemical Selection Subgroup for consideration for retest. Some probably will go through the whole process again, but this time under the new standards and tightened procedures.

A second equivocal finding, which Brown and his colleagues fully expect if the substance turns out to be a weak carcinogen, will put more pressure on the Risk Assessment Subgroup, which has to tell the public if the chemical is a hazard to humans. The regulatory agencies also will feel the increased pressure, particularly if the equivocal finding is made on a product that enjoys widespread use.

BROWN, WOLFE DISAGREE SHARPLY WITH NCI STAFF, SUBGROUP ON DICHLORVOS

Arnold Brown differed sharply with the Clearinghouse Data Evaluation/Risk Assessment Subgroup and with NCI staff over the staff's interpretation of the results of tests conducted on the chemical dichlorvos.

The report on dichlorvos bioassay concluded that there was insufficient evidence to support its carcinogenicity "under the conditions of the test." The chemical is used as an insecticide in agriculture and homes, including aerosols.

Brown and subgroup member Sidney Wolfe disagreed, and Brown filed a minority report after the subgroup voted 8-2 to accept the report. The subgroup later voted unanimously to refer dichlorvos back to the Chemical Selection Subgroup for consideration for additional tests.

Bioassay Program Director Richard Griesemer told the subgroup that dichlorvos was fed at two dose levels to Osborne-Mendel rats and $B_6C_3F_1$ hybrid mice. Because of the chemical's instability, diets were

changed daily. The treated animals were exposed for 80 weeks and then held an additional period for observation. Most of the animals survived the two year study period.

In the treated mice, two squamous cell carcinomas and one squamous cell papilloma of the esophagus were found, as well as areas of focal hyperplasia of the esophageal epithelium. These lesions were absent in control animals.

Griesemer pointed out that spontaneous squamous cell carcinomas of the esophagus have been found in the hybrid mouse, but their general incidence is unknown because of past variations in the pathology protocol. In two treated rats, nonneoplastic proliferative lesions were seen in the squamous epithelium of the upper gastrointestinal tract and an epithelial hyperplasia of the esophagus in another rat.

Malignant fibrous histiocytomas also were found in a number of treated rats, but they were not considered to be significant, Griesemer said.

Wolfe, who was the primary subgroup reviewer of the study, was critical of the small number of matched control animals that were used. He referred to several pathologic findings not mentioned by Griesemer which Wolfe considered significant. He mentioned two other long term studies of dichlorvos and the similarities in the findings between them and the NCI bioassay. Wolfe pointed out that cichlorvos is a mutagen in microbial systems. The Environmental Protection Agency is reviewing dichlorvos and its mutagenicity is one factor being considered.

Clearinghouse member Marvin Kuschner commented that in cases in which there is a steep dose response curve, there is the possibility of missing a carcinogenic effect when a highly toxic chemical is tested at the maximum tolerated dose for an animal's lifetime. It may not be possible in such tests to administer a high enough dose for an adequately prolonged period to induce a carcinogenic response, Kuschner said. He suggested that it may be more appropriate to expose animals for a short duration at toxic levels than at lower doses for their lifetime, and that dichlorvos might be a candidate for that type of test.

Subgroup member Michael Shimkin suggested that any retest should try to develop data on the mechanisms of action of dichlorvos and should include a range of dose levels.

Subgroup member John Weisburger argued that the dichlorvos study was proper in the sense of a classical bioassay. Since no significant findings were discovered, Weisburger said he concluded that dichlorvos was not carcinogenic under the conditions of the test. Subgroup members discussed the interpretation of the increased number of tumors found in treated animals as opposed to controls. Cuyler Hammond suggested that the spontaneous incidence of esophageal tumors could be estimated by examining the geneology of the experimental animals.

But Brown then made a motion that the dichlorvos study was properly designed and conducted to provide information on its carcinogenicity. It was seconded by Weisburger but was defeated. Gerald Rowe then moved that the report be accepted, and Shimkin seconded it. It was noted in the discussion that the report points out the uncertainties in the study which must be taken into account in interpreting the results. Brown and Wolfe cast the only votes against the motion.

Wolfe argued that if there was insufficient evidence to indicate the association of the esophageal tumors with dichlorvos because of the lack of control data, as stated in the report, conversely it could not be said that the tumors were not related to dichlorvos. He added that the same argument applied to the malignant histocytomas in the treated rats.

Brown said that because of the rarity of epithelial tumors of the esophagus, those found in the test animals were probably treatment related.

Subgroup member Louise Strong moved that, in view of dichlorvos' reported mutagenicity, its chemical nature and the appearance of "extremely rare tumors" in treated animals in the NCI bioassay, it be referred to the Chemical Selection Subgroup for consideration for retest. Although Griesemer expressed concern that the subgroup had not given enough guidance in its referral, particularly to the type of testing that should be done, the motion was approved unanimously.

In his minority report to James Peters, director of the Div. of Cancer Cause & Prevention, Brown wrote:

"It is my belief that the presence of a carcinoma of the esophagus in the strain of animal used is a highly significant lesion. I come to this conclusion on the basis of the rarity of esophageal carcinomas in control animals both test and historical. The fact that dichlorvos is having an effect on the esophageal epithelium is confirmed, in my view, by the reports of epithelial hyperplasia. An additional source of concern is the fact that dichlorvos has been shown to be mutagenic in the salmonella test system."

In other actions on bioassay reports, the subgroup concluded that one chemical—procarbazine—was a carcinogenic risk to humans; that another—lindane—was not, based on the NCI bioassay; and that the test results on four others did not provide sufficient data to determine either way.

Hammond, who reviewed the procarbazine report, said that although there was an inadequate number of control animals in the test, it made no difference since procarbazine was clearly carcinogenic in both sexes of rats and mice. He said that procarbazine is usually given at acute toxic dosages when used as a chemotherapeutic drug.

Shimkin, who reviewed the lindane report, said that the only statistically significant result was the occurrence of an increased incidence of hepatocellular carcinomas in the low dose male mice. From the

chemical structure of lindane, Shimkin said, it would be expected that it would affect the liver but he did not believe the evidence supported the carcinogenicity of lindane. It was pointed out in the discussion that other mice studies indicated lindane to be carcinogenic, but the subgroup finding would have to be based only on the NCI bioassay. Lindane is an organic pesticide used in agriculture, and also appears in some pharmaceutical preparations.

Subgroup member Henry Pitot reviewed the report on phosphamidon, an organophosphorous compound used as an insecticide, particularly as a crop duster. Survival of the rats and mice was considered adequate. No significant differences in tumor incidence was found between the treated hybrid mice and control animals. In the treated rats, a statistically significant increase was reported in the incidences of hemangiosarcomas of the spleen and in C-cell adenomas of the thyroid.

Pitot pointed out that the incidence of C-cell adenomas was at least as high in the control rats used in the dichlorvos bioassay, as well as in controls used in another study reported in the literature. The dichlorvos control rats also had an incidence of hemangiosarcomas of the spleen which approached the incidence found in the treated phosphamidon animals.

Griesemer commented that the findings of two different tumor types of borderline significance, as opposed to only one, resulted in the conclusion that phosphamidon was carcinogenic in rats. Based on the data, Pitot said, he was not prepared to classify phosphamidon a carcinogen. He suggested that phosphamidon might promote the incidence of spontaneously occurring tumors. Kenneth Chu, NCI staff member, said that the difference between the dichlorvos and phosphamidon controls could be related to variations associated with the diagnostic pathologists. Jerrold Ward, NCI, said that the differences in tumor incidences could have resulted from random variations in animals or from missing tumors when selecting or processing tissues. Although pathologists may use varying terms for the same lesion, Ward said, differences in incidences probably were not related to variations in the ability of diagnostic pathologists to detect tumors.

Weisburger questioned the significance of the dose related trend reported for the tumors found in the treated rats. He emphasized the need to compare the treated animals with a national pool of control data, the only way that tumors occurring in low incidences can be properly evaluated, he said. Griesemer said such a data base would not be available until after the backlog of studies had been evaluated.

Pitot moved that the results should be considered equivocal and therefore no conclusion drawn on the carcinogenicity of phosphamidon. The motion was approved unanimously.

Strong, reporting on the dapsone bioassay, said there was a dose related increase in the incidence of stromal tumors in treated male rats. Tumors were found in the abdominal organs and the peritoneal tissues. Similar tumors were not observed in either female rats, mice or historical control animals. Strong agreed that the tumors in the male rats probably were treatment related but expressed doubt that a human risk assessment could be made on the basis of a carcinogenic response in only one strain and sex, adding that other data, such as from in vitro studies, would be necessary to assess risk. The subgroup agreed unanimously. Dapsone is a major therapeutic agent in treatment of leprosy, malaria, and certain gynecologic disorders.

Griesemer, reporting on the captan bioassay, said there was a statistically significant increase in the incidence of tumors in the duodenum of the captan treated mice, although the actual number of tumors was quite small. Weisburger pointed out the increased incidence of adrenal cortical tumors found in the treated female rats, but they were not considered significant. Brown moved that the risk assessment could not be made because of the unusual nature of the tumors associated with captan treated mice, and it was approved unanimously. Captan is a fungicide, used on foods, plants and in soaps.

Weisburger reviewed the report on the trisodium ethylenediaminetetraacetate trihydrate (EDTA) bioassay. He said that when this bioassay was originally designed, it was to serve as a control study to the one conducted on NTA. It failed as a matched control because the dose levels of EDTA were approximately three times too low. He said that the lack of a significant growth depression in the treated animals also indicated that the dose levels were not high enough, and that no treatment related tumors were found in either rats or mice. EDTA is a food additive used to sequester trace metals.

Rowe added that EDTA and similar substances upset the ionic balance in animals; therefore, any results on the carcinogenicity of such substances are open to considerable question. The subgroup agreed to accept the report and refer EDTA to the Chemical Selection Subgroup for retesting at levels equivalent to those in the NTA study.

A report on the photodieldrin bioassay was ready, but the subgroup agreed that it should be considered at the time dieldrin studies are reported on. NCI staff had reported that under the conditions of the test, photodieldrin was not carcinogenic in rats or mice. Rowe, who reviewed the report, said there was an inadequate number of matched controls in the test but agreed with the staff conclusion.

CONTRACT AWARDS

Title: Review of cancer education in medical, dental and osteopathic schools, renewal

Contractor: American Assn. for Cancer Education, $52,008.

Title: Isolation and tissue culture of human tumor cells, continuation

Contractor: Sloan-Kettering Institute for Cancer Research, $221,262.

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Their addresses, all followed by NIH, Bethesda, Md. 20014, are:
Biology & Diagnosis Section — Landow Building
Viral Oncology & Field Studies Section — Landow Building
Control & Rehabilitation — Blair Building
Carcinogenesis Section — Blair Building
Treatment Section — Blair Building
Office of the Director Section — Blair Building
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CB-84238-34

Title: *Lipid levels and cheolesterol metabolism in relation to human breast cancer risk*

Deadline: *Jan. 20, 1978*

The Breast Cancer Task Force, NCI, is interested in seeking investigators to study the correlation, if any, between human breast cancer risk and lipid levels and/or cholesterol metabolism. Principal objectives of the project are: 1) to examine a possible etiologic role of lipid(s) in contributing to patterns of breast cancer appearance and 2) to investigate cholesterol metabolism and kinetics in relation to risk of breast cancer development. A proposal could respond to either objective or to both. Any approach will be considered, and the project could originate from one or a number of collaborating institutions.

RFP NCI-CB-84237-34

Title: *Epidemiology of spontaneous mammary tumor in dogs: Modification of incidence by experimental intervention*

Deadline: *Jan. 20, 1978*

The Breast Cancer Task Force is seeking investigators to study conditions necessary to modify experimentally the incidence of spontaneous mammary tumors in dogs. In view of the epidemiologic similarities between mammary cancer in dogs and in humans, the dog appears to afford a promising model system in which to study experimental dietary or hormonal intervention and the effects on mammary cancer incidence. A study could, however, address instead other experimental modifications of factors involved in breast cancer risk. Access to a population-based canine tumor registry would be highly desirable, and the proposal could originate from one or a number of collaborating institutions. Any approach will be considered provided it enhances our understanding of the etiology of human breast cancer.

RFP NCI-CB-84222-34

Title: *Isoproteins in normal, benign and malignant breast tissues*

Deadline: *Nov. 22*

The Breast Cancer Task Force is seeking investigators to identify and characterize various isoenzymes or isomeric proteins (e.g., isoferritin) in normal, benign and neoplastic breast tissue. Of particular interest will be the identification of various isoproteins unique in type or amount in neoplastic breast tissue.

RFP NCI-CB-84229-34

Title: *Interrelationships among diet, steroid hormone metabolism and human breast cancer*

Deadline: *Nov. 21*

The Breast Cancer Task Force is seeking investigators to study possible correlations between metabolism of steroid hormones, as influenced by the diet, and incidence of human breast cancer. Rates of production, secretion, and metabolism of reproductive hormones should be defined in relation to dietary changes; of interest is the possible role of particular dietary components, such as fat, cholesterol, animal protein, etc. Changes in dietary habits could be explored in migrants moving to another culture or other groups of individuals adopting a markedly different dietary lifestyle, or in populations in which environmental, historical or medical conditions have imposed dietary modifications. The dietary and hormonal parameters could be explored as possible risk factors for the development of breast cancer.

RFP NCI-CB-84228-34

Title: *Prognostic significance in breast cancer of the immunological response of cells from regional lymph nodes*

Deadline: *Nov. 22*

The Breast Cancer Task Force is seeking investigators to study the immunologic response of cells from lymph nodes obtained at time of mastectomy. The major objective of the investigation is the possible prognostic application of the findings to breast cancer. The responding agency should have available sensitive and specific assays for immunologic activity of lymph node cells. Responding agencies should also demonstrate availability of suitable patient population and follow-up capability. The purpose of this project is to determine the usefulness of such assays in predicting recurrence of breast cancer.

RFP NCI-CB-84224-34

Detection of antigen-antibody complexes in sera of patients with breast cancer
Nov. 22

The Breast Cancer Task Force is seeking investigators to study the application of assays for circulating antigen-antibody complexes in sera for the diagnosis and monitoring of human breast cancer. Re-

sponding agencies should have experience with the assays and should have some preliminary evidence of their efficacy in discriminating normal from benign and/or malignant breast disease patients. Detailed summary of such evidence must accompany the proposal.

RFP NCI-CB-84223-34

Title: *Biologic biochemical and immunologic characterizations of "premalignant" human mammary epithelial hyperplasias*

Deadline: *Jan. 5, 1978*

The Breast Cancer Task Force is seeking investigators to delineate differences and similarities in biologic, biochemical and immunologic parameters among different types of hyperplastic epithelial lesions of human mammary ducts, lobules and invasive breast cancers. The ultimate goal would be to discover characteristics associated with malignant potential and to be able to identify lesions possessing these characteristics at a preinvasive stage. Responding institutions should have access to large numbers of biopsy specimens, and techniques for handling the experimental materials should be clearly outlined.

Any combination of study components will be considered. A proposal may originate from one or a number of collaborating institutions. The project will be a two to three year incrementally funded program depending on the scope of work.

RFP NCI-CB-84230-34

Title: *Relationship between thyroid diseases and breast cancer*

Deadline: *Nov. 21*

The Breast Cancer Task Force is seeking investigators to study the relationship of thyroid diseases to breast cancer. The study should be designed to ascertain the incidence of breast cancer in cohorts of women with well defined thyroid diseases and in appropriate controls. Proposals should include the diagnostic procedures followed in defining the thyroid abnormalities as well as the modes of treatment. The proposal could originate from one or a number of collaborating institutions.

RFP NCI-CB-84231-34

Title: *Benign and non-invasive breast lesions in populations at different risk for breast cancer*

Deadline: *Nov. 21*

The Breast Cancer Task Force is seeking investigators to study the frequency, pathologic spectrum, and epidemiologic characteristics of benign, hyperplastic, and non-invasive breast lesions in populations which have large differences in breast cancer risk, including, in particular, populations at low risk. While the incidence and epidemiologic aspects of breast cancer itself have been extensively studied in many different populations, our understanding of the incidence patterns, pathologic spectrum, and epidemiology for benign lesions, particularly in populations at low risk for breast cancer, is not as well developed and is an important area for investigation. The major objective of the project is to increase our understanding of the relationship between potentially preneoplastic breast lesions and breast cancer itself through a study of the incidence patterns, pathologic characteristics, etiologic factors, and any other parameter that the investigator deems important, for benign breast lesions in populations with major differences in breast cancer risk.

Contract Specialist for the above nine BCTF RFPs: E.J. Abbott
Biology & Diagnosis
301-496-5565

RFP NCI-CB-84220-32

Title: *Comparison of surgical castration with chemotherapy as adjuvants to mastectomy for stage II cancer of the breast*

Deadline for Receipt of Resumes: *Sept. 19*

The Breast Cancer Task Force is interested in institutions which can study a minimum per/year of 50 premenopausal patients who have histologic stage II breast cancer (T2 or less with metastases to one or more ipsilateral lymph nodes) and have positive estrogen receptor determinations. The patients are to participate in a two-armed, randomized, prospective, controlled clinical trial which compares a chemotherapy program (cytoxan, methotrexate, 5-fluorouracil) with surgical castration as adjuvant to mastectomy. In order to enter the required number of patients (150 for the two treatment groups combined) over a three-year period, a multi-institutional cooperative effort may be necessary, although a single or small number of participating institutions would be preferred. All estrogen receptor determinations on the breast cancer tissues should be made by a single laboratory using an approved method. Although not essential, assays for other hormone receptors will be of interest.

Respondents should document in four pages or less: (1) their willingness and capabilities to conduct such a study; (2) the availability of appropriate patients in their institution(s); and (3) the willingness of patients to participate in this study. Documentation of appropriate patients for entry into the study must be limited to those meeting the eligibility requirements—(1) premenopausal; (2) positive axillary lymph nodes; (3) estrogen receptor (ER) positive or, if ER determinations have not been performed routinely, an estimation of the number of ER positive, otherwise eligible patients. Appraisal of the subjects' willingness to participate might be obtained from a poll of 100 women with characteristics (age, ethnic origin, socioeconomic status, etc.) similar to those of the projected study group. Tabulation of responses should indicate the numbers of those who

would agree, those who would refuse, and those who would refuse because they favored one of the treatments or because they wanted neither of these treatments.

Twenty copies of the resume of capabilities must be submitted with the request for the RFP.

RFP NCI-CB-84221-32

Title: *Is the effect of chemotherapy on stage II breast cancer due to alterations in hormonal status?*

Deadline: *Nov. 28*

The Breast Cancer Task Force is interested in institutions that can design and carry out investigations which will show whether the apparent prolongation of clinically disease-free interval produced by adjuvant chemotherapy for stage II cancer of the breast is mediated: (1) through direct cytoxic effect on the cancer; (2) through indirect cytotoxic effect on endocrine organs; or (3) through a combination of these effects.

The observations that adjuvant chemotherapy appears more effective for premenopausal than for postmenopausal patients and that about 80% of the premenopausal women underwent cessation of menses during prolonged therapy with phenylalanine mustard (L-PAM) or with combined cyclophosphamide, methotrexate, fluorouracil (CMF) have led to the theory that chemically induced castration is responsible for the prolongation of the recurrence-free period. Although the qeustion is a clinical one, the Breast Cancer Task Force would consider laboratory experiments and combined laboratory-clinical investigations as well as exclusively clinical studies. This would include consideration of animal experiments and of experiments in which human tumors are grown in animals or as tissue cultures. It is anticipated that one or two awards will be made and that up to three years may be required to accomplish a project.

Contracting Officer for the above two RFPs: Phillip Webb
Biology & Diagnosis
301-496-5565

RFP NCI-CB-84227-37

Title: *Metabolism of polycyclic aromatic hydrocarbons in the induction of mammary tumors*

Deadline: *Nov. 15*

The Breast Cancer Task Force is interested in establishing a contract with organizations having the capabilities to carry out research in the metabolism, the disposition, and the elimination of carcinogenic polycyclic aromatic hydrocarbons (PAH) in animals. Metabolism in the mammary glands, liver and other organs also is of interest, as well as comparative studies of animals at certain ages or of certain strains that are resistant to such PAH induction of tumors.

RFP NCI-CB-84226-37

Title: *Development of an assay for genetic damage to mammary gland cells*

Deadline: *Nov. 15*

The Breast Cancer Task Force is interested in establishing a contract with organizations having the capabilities to carry out a research and development program to devise the means for detecting genetic damage or the changes that may increase the rate of genetic damage in mammary cells. The long-term objective is to acquire the ability to correlate the rate of genetic damage with the rate of mammary cell transformation, thus, to obtain early warning information about enhanced risk of mammary cancer in vivo.

RFP NCI-CB-74225-37

Title: *Produce and identify antibodies to types of collagen, procollagen and/or metabolically related enzymes*

Deadline: *Nov. 15*

The Breast Cancer Task Force is interested in establishing a contract with organizations having the capabilities to carry out a research and development program to identify and produce specific antibodies to various mammalian collagen and procollagen types and/or metabolically related enzymes. Responding persons must include a description of the procedures to establish the quality and specificity of the antibodies and estimate the quantities that can be made. The antibodies produced will be made available to investigators engaged in studies bearing on the ability of breast cancer cells to stimulate collagen production or enzymes involved in degradation.

Contract Specialist for above three RFPs: Robert Stallings
Biology & Diagnosis
301-496-5565

RFP NIH-ES-78-5

Title: *Microbial mutagenesis testing*

Deadline: *Oct. 21*

The National Institute of Environmental Health Sciences is interested in receiving contract proposals from organizations with the interest and capability to successfully conduct the studies proposed for this contract. NIEHS proposes research for the testing of industrial and environmental chemicals for mutagenic activity using bacterial assay systems both with and without metabolic activation. Seventy-five to 100 compounds per year will be tested in a blind study. Offerors should possess demonstrated experience and proficiency in chemical mutagenesis using various bacterial systems. It is estimated the project will require about four years to complete. Enclose a self-addressed label with request for the RFP.

National Institutes of Health
Research Contracts Branch, DCG
Attn: F.L. Suggs, Building 31 Rm 1B38
Bethesda, MD 20014

SOURCES SOUGHT

Project No. NCI-CP-FS-71054-55

Title: *Studies on environmental cancer utilizing a pre-paid health plan*

Deadline for Receipt of Statement of Capability: *Sept. 6*

Organizations are sought having a pre-paid health plan (PPHP) operation of specific population size, specific years of operation, and extensive computerization of data, which have the capability of engaging in collaborative research to test specific hypotheses concerning cancer. Only those pre-paid health plans having the very specific requirements need reply, as no others will be considered, and those not deemed to meet the requirements will not receive an RFP.

The specifications are as follows:

1. The pre-paid health plan staff should be knowledgeable and experienced in cancer and in data collection and management. They should be willing to collaborate closely with the NCI project officer in designing studies, and collecting and analyzing data that test hypotheses of importance to the NCI. The PPHP should already have all the computer equipment on hand.

2. If necessary, in order to achieve the large numbers of cases required to test a specific hypothesis, the PPHPs as requested by the project officer, may pursue common protocols for studies requiring much larger base populations.

3. The base population of the PPHP should be over 150,000 individuals, and the plan should have been in existence for a period of 15 years or more.

4. The health records of the PPHP should consist of unit longitudinal records which provide information concerning all contacts made with the health plans, including therapeutic drugs, clinical conditions, surgical procedures, pathological diagnoses, occupation over the years, and location of residence.

5. The availability of additional personal information such as cigarette smoking, alcohol consumption, other risk factors, socioeconomic status, and special data would be advantageous, but not necessary.

6. There should be accurate age, sex, and time-specific information for the entire health plan membership, so that rates can be calculated for specific cancers.

7. There should be some simple means of identifying cancer cases, such as a tumor registry or its equivalent.

8. The computerized PPHP records should allow rapid choice of controls which could be matched to the patients on the basis of age, sex, duration of PPHP membership and level of coverage. Systems that allow matching of other characteristics are not necessary but would be advantageous.

9. While emphasis will be on case-control studies involving record reviews, the contractor should be capable of collaborating in interview and/or cohort studies if these are indicated after analysis of the case-control studies. More than one award may be made, to separate organizations, and the length of time for the research in each may be three years.

Specific hypotheses of major interest to NCI for the first year will be given in the RFP. (Example: the relationship between menopausal estrogen use and ovarian cancer). Studies for the succeeding two years will be based on results of the first year's work, and therefore officially will remain open at the time of award.

Organizations which meet the above criteria and which are interested in competing should send 12 copies of their submission. The information submitted should be concise, should indicate clearly how the organization meets the stated criteria or requirements, and should include curricula vitae or resumes only of those professional personnel who will be assigned to the contract.

Project No. NCI-CP-FS-71041-55

Title: *Study of the familial aspects of colon-rectal cancer in two rural Nebraska counties with unusually high rates for these tumors*

Deadline for Receipt of Proposals: *Sept. 6*

Requirements for this project include: (1) demonstrated expertise in large scale family studies (minimum of 100 families to be studied); (2) availability of appropriate support services including trained interviewers, statisticians with experience in genetic studies, computer facilities and laboratory backup; (3) an effective working relationship with state and local health officials; and (4) close geographic proximity to the study counties to minimize logistic problems and travel expenses. NCI knows of only one source in a position to meet these specialized requirements—Creighton Univ., Omaha, Neb. Those organizations that can meet the requirements stated above are invited to submit statements of capabilities. Mail five copies of resume.

Contracting Officer for the above two projects: Fred Shaw
Viral Oncology & Field Studies
301-496-1781

The Cancer Letter —*Editor* JERRY D. BOYD

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