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NCAB, DRCCA BOARD ASKED TO CONSIDER DROPPING ALL STAFF INVESTIGATOR SALARY SUPPORT FROM CORE

Cancer center executives concerned about the effect of restrictions against paying staff investigator salaries from core grants have further cause for concern following discussion of new core grant guideline proposals at last week's meeting of the National Cancer Advisory Board.

The Board's Subcommittee on Centers & Construction had recom-

(Continued to page 2)

In Brief

BENACERRAF, SNELL, DAUSSET WIN NOBEL PRIZE; AACE SEEKS INCREASE IN CLINICAL EDUCATION FUNDS

TWO AMERICAN scientists—Baruj Benacerraf, president of the Sidney Farber Cancer Institute, and George Snell, senior staff scientist emeritus of Jackson Laboratory—will share the 1980 Nobel Prize in medicine with Jean Dausset, of Paris Univ. In announcing the award, the Royal Caroline Institute of Medicine cited their work on "genetically determined structures on the cell surface that regulate immunological reaction." The three work separately but are aware of each other's research. Benacerraf is chairman of the pathology department at Harvard Medical School and became president and chief executive officer of Farber last July. . . . **AMERICAN ASSN.** for Cancer Education has asked NCI Director Vincent DeVita to review allocations planned for clinical cancer education grants in the FY 1981 budget. The original White House budget had asked $10 million for clinical education, down nearly $1 million from 1980 and $1.4 million from 1979. When the President slashed NCI's budget request to $965 million in his ill-fated anti-inflation effort, clinical education was cut further, to $8 million. The House restored most of the cuts in its appropriations bill, but clinical education was left at $8 million. The AACE letter to DeVita noted that only 17 of 34 approved competing applications can be funded. "It must be remembered that the goals of this program are not only to augment manpower but they are also to assure the continuing improvement of knowledge and attitudes of professional students pertaining to cancer," the letter said. "The need to enlarge and improve cancer education of tomorrow's physician continues to be present. Competition for curricular time and the absence of departments of oncology in the vast majority of professional schools hamper cancer education planning in the absence of support of interdisciplinary coordination provided by these grants." The letter was signed by Robert Madden, AACE president; Daniel Hays, president elect; and advisory council members V.K. Vaitkevicius, Richard Bakemeier, Mario Martinez, and John Foley.

NCAB MEMBER ROWLEY ASKS ELIMINATION OF STAFF INVESTIGATOR SALARY SUPPORT

(Continued from page 1)

mended to the Div. of Resources, Centers & Community Activities Board of Scientific Counselors that it consider accepting the NCI staff proposal that an upper limit of 35 percent of an investigator's salary be placed on the amount that could be paid from the core grant (*The Cancer Letter*, Oct. 3).

When the subcommittee's recommendations were discussed by the NCAB last week, NCAB member Janet Rowley asked that the possibility of abolishing staff investigator salary support entirely from the core grant be considered.

"In my view, the full amount of an investigator's salary should be included in the R01 or P01 grant," Rowley said. "The time of peer review is the best place to determine if the amount requested is appropriate. . . . If an investigator requests 100 percent effort and salary in the R01 application, peer review can look at it, determine perhaps that there is no need for 100 percent effort, and cut it to 25 percent (or any figure reviewers deem appropriate). There is no such control over core salary support."

The current guidelines provide no guidance beyond the requirement that the amount of salary support bear a direct relation to the percent effort devoted to funded peer reviewed research support and to management of center activities. Under this condition, requests for staff investigator salary support are not reviewable.

A few centers have sought to take advantage of that in their renewal applications, resulting in huge increases in funds requested. The Cancer Center Support Grant Review Committee has had no choice other than to go along. So far, the situation has been tolerable, but NCI feels it soon will get out of hand.

The staff proposal to limit core salary support to 35 percent was an effort to put a lid on those expenditures. But Rowley and other NCAB members feel that rather than serve as a limit, the ceiling would immediately become a floor and result in doubling or tripling the amount of salary support now being provided by center core grants.

Core salary support now amounts to 10-15 percent of the total core budget of $68 million, according to NCI staff estimates, or from $6-10 million. If every center requested 100 percent support, the figure would be "frightening," Centers Program staff member Ray Morrison said—about $60-70 million.

If every center received salary support funding at the 35 percent limit, that would amount to about $22 million, NCAB Chairman Henry Pitot pointed out. "The present situation is less bad than it would be if everyone came in with 35 percent," Pitot said.

"And everyone will if we establish a ceiling," NCI Director Vincent DeVita added.

"If we are locked in to 35 percent, it could lead to a horrendous situation," Rowley said.

"I personally support Dr. Rowley's position," NCAB member Maureen Henderson said. "In my institution, it is always better accepted if all salaries are on peer review."

"Some portion of salary support may be necessary," NCAB and Cancer Panel member Harold Amos said.

The guideline proposal provides for payment of three fulltime equivalent administrator salaries, plus short term support for new investigators and those between grants, and there have been no objections to that. At issue is salary support for established investigators with their own grants or contracts.

"We would like to see the Centers Program strengthened, not dissipated," Henderson said. "It would be tragic if the (35 percent) limit results in increased staff investigator salary support. It is our intent to contain those costs."

NCAB member Rose Kushner suggested that some services now funded by core grants should be supported by R01 or P01 grants.

"The function of the core grant is to provide central services and resources," Pitot said. "If you eliminate those and eliminate staff investigator support, you might as well eliminate core grants."

Pitot asked Rowley if she cared to offer an amendment to the subcommittee's report recommending that all staff investigator salary support be dropped from the new guidelines.

"No, I just wanted to express my concern and request consideration."

The DRCCA Board of Scientific Counselors' Centers Subcommittee will review the guideline proposals and the NCAB report at a meeting prior to the next meeting of the full Board, scheduled for January.

The NCAB subcommittee will have an opportunity to consider the DRCCA Board recommendations, with the issue tentatively going to the full NCAB again next May.

NCAB DEFENDS ORGAN SITE PROGRAM, DEVITA TO DISCUSS IT WITH PANEL

NCI's Organ Site Program, whose participants have felt themselves somewhat beleaguered with level or slightly reduced budgets and hints from the NCI director that some parts of the program might be phased out, received a vote of confidence from the National Cancer Advisory Board last week.

The Board unanimously accepted a report by its Subcommittee on Organ Sites, chaired by William Powers, which concluded:

"The subcommittee addressed the question of whether the Organ Site Program should be phased out. It was unanimously concluded that such a move would be premature and that a decrease in the level

of investigational effort would probably result. Furthermore, the subcommittee notes that funding for the Organ Site Program has leveled off. Recognizing the pressures on the NCI budget and the fiscal austerity to which all programs are being subjected, it is hoped that adequate funds will continue to be made available without reduction in order to keep this successful program viable.

"In concluding this report, the subcommittee recommends continuance of the Organ Site Program and continued surveillance by the NCAB Subcommittee on Organ Site Programs."

Prior to the Board meeting, the subcommittee had reviewed the National Prostatic Cancer Project, one of the four grant supported projects which make up the Organ Site Program (the others: National Bladder Cancer Project, National Large Bowel Cancer Project, National Pancreatic Cancer Project). Those four are grant supported, each with planning, direction and coordination and grant review provided at a headquarters institution away from NCI. The Breast Cancer Task Force is directed by NCI and supports research with contracts as well as grants; it is not a part of the Organ Site Program, although the NCAB subcommittee has reviewed it in the past.

Gerald Murphy, project director of the National Prostatic Cancer Project, discussed the status of NPCP with the subcommittee, Powers' report said:

"The NPCP currently supports epidemiologic, laboratory, and clinical studies encompassing the areas of etiology and prevention, detection and diagnosis, and treatment. An effective multidisciplinary research plan with work plans and well defined priorities has been developed. The project has succeeded in stimulating new investigative efforts where previously there had been little, and is attracting new investigators to address the problems of prostatic cancer.

"A number of previously unavailable resources have been developed and have been made accessible to the research community. These include a tissue bank, serum bank, cell lines and animal models. These resources are being used to characterize and better understand this tumor. New and promising diagnostic tests are being developed and field tested. A successful preclinical and clinical treatment program has been developed. To date, the project's cooperative group has accessioned over 1,500 patients to 13 protocols among 10 institutions. These are but a few examples of current activities that were reported to the subcommittee.

"The results of these activities are effectively communicated to the biomedical community. An extensive publication record in peer reviewed journals has been compiled. Workshops addressing specific problems have been held and several monographs have resulted. These workshops have attracted numerous laboratory and clinical investigators to address these problems and develop new approaches.

"The NPCP was invited to participate (at no cost to NCI) in an international symposium which attracted nearly 700 attendees from 29 countries. Communication is also effected through a quarterly newsletter published at no cost to NCI. For FY 1980, NPCP activities were supported at $4.7 million. This accounts for about 60 percent of NCI's total efforts in the area of prostatic cancer.

"The subcommittee unanimously accepted Dr. Murphy's report. The project appears to be operating successfully and is being effectively administered. This subcommittee review follows earlier reviews of the Bladder and Large Bowel Projects, as well as an earlier review of the Breast Cancer Task Force when Dr. Irving London chaired the subcommittee. These reviews have found these organ site programs to be effective and successful. They are attracting new investigators, stimulating new research, establishing effective communication between laboratory and clinical scientists, and communicating research opportunities, needs, and discoveries in the scientific and medical community."

NCI Director Vincent DeVita admitted, "I'm the one who started the rumors about phasing out organ site programs." It was not really a rumor but a statement by DeVita to the Board earlier this year and later to ***The Cancer Letter*** (July 25) to the effect that organ site programs might be called upon to justify their continued existence.

"The organ site programs were started to stimulate interest in particular areas where not much work was being done," DeVita said to the Board last week. "Without addressing whether they are good or bad, we should go beyond that and ask, what is the end point? The Breast Cancer Task Force budget is $12 million, but the total NCI is spending on breast cancer research is now $47 million. There's no question it has stimulated the field. I would be interested in hearing from people in the task forces when they feel their job has been finished."

If the decision on whether to continue an organ site program "is left to people in the programs, they will never end," DeVita said.

Powers responded that he is not supported by or connected in any way with any of the organ site programs. He said Murphy had noted that a significant part of the NPCP was the communications and planning. "He expressed the concern that if the prostatic project is ended, the money might go into other pockets."

The subcommittee has been restrained in its support for the Organ Site Program, Powers said. It recommended against initiating one program (on head and neck cancer) and recommended the phasing out of another (on lung cancer).

Board member Irving Selikoff asked if the existence of the task forces "increases the likelihood of

better review?" Powers responded, "That question is probably the primary reason for the NCAB Subcommittee on Organ Sites. We made every effort to compare the quality with other grant areas, and the quality of review. We concluded that organ site grants were at least the equivalent of others. The programs are turning down more and funding at lower rates than are the R01 study sections."

The organ site programs exist to combat the four or five major cancer killers, Powers said. "Colorectal, breast, prostatic, pancreas, bladder cancers are the important killer diseases. Lung cancer is, too, but that was phased out because the program was bad."

"I'm not against working on prostatic cancer or any of these," DeVita said. "We have an enormous amount of work going on in lung cancer. It doesn't need stimulation."

Board member Sheldon Samuels, referring to DeVita's question on when an organ site program completed its job, offered, "When it has created a claque to defend itself." But Board member LaSalle Leffall said, "An organ site program has done its job when there is a substantial decrease in mortality" in that particular disease.

"I'm unhappy that we have become advocates for special interests," Board member Maureen Henderson commented.

"We're not advocates for special interests but to meeting special needs," Powers answered.

Panel member Harold Amos said, "There are other strong interests, people interested in tumor viruses, immunology, and other areas. The Organ Site Program was formed because no one was interested in those fields. If we have succeeded in bringing them into the fold and they can compete in the hurly burly, fine. But I don't think we're there yet."

"May I propose another task force?" Selikoff asked. "Part of our job is to identify other areas of need and opportunity." The area he suggested: The increasing incidence of cancer among blacks and other nonwhite Americans.

"This is an important area for investigation of environmental, diet, lifestyle, and occupational causes," Selikoff said.

Board Chairman Henry Pitot suggested that it would be an appropriate subject for the Subcommittee on Organ Sites to consider.

Selikoff said the higher incidences now being reported among nonwhites "may be environmental, related to population shifts, diet, better reporting, better diagnosis than in the past. We don't know. NCI should direct itself to this problem."

DeVita said he had planned to "broach the issue of the Organ Site Program" with the President's Cancer Panel. "I assume that acceptance of the (Powers) report by the Board will not preclude me from discussing this with the Panel."

The Organ Site Program is housed in the Div. of Resources, Centers & Community Activities. The DRCCA Board of Scientific Counselors had some comments on the program when it was described at the new BSC's initial meeting:

Andrew Chiarodo, acting branch chief: Organ site programs were never intended to be a substitute for R01s but to complement them.

Harry Eagle: How do you handle grant applications from members of the working cadre (who review the applications)?

Chiarodo: The review in those cases is done by an ad hoc committee with less than 50 percent membership from the cadre.

Ernst Wynder: The emphasis is on treatment rather than etiology. There is no question that if you take 13 people, nine of them surgeons, you'll have clinical trials. The Organ Site Program has not been giving proper emphasis to etiology and that can be corrected by appointing more epidemiologists to the committees.

William Terry: As you get up speed and become comfortable (as members of the BSC), express yourself on the issue of the NCAB vs. this Board with regard to oversight of the Organ Site Program. What are the justifications for a mechanism to focus on an organ? As opposed to the conventional mechanisms?

Charles Moertel: What are the relative priority scores necessary for funding an R01 vs. an organ site grant?

Chiarodo: About the same.

Peter Greenwald: Once you have the score, can you fund down further?

Chiarodo: No, our cutoffs are more stringent.

Eagle: But two different groups could assign different scores to the same grant.

Moertel: How do the cost per patient (in organ site clinical trials) figures compare with the Cooperative Groups?

Chiarodo: A number of the groups do have protocols now in organ site areas. Prostatic Cancer Project trials cost $1,100 per patient, which I think compares favorably with the groups.

Lester Breslow: There is a certain attractiveness to the organ site approach we ought not to ignore.

Wynder: I am in favor of coordinated research. Structured research has a place in the Cancer Program.

In FY 1980, the Organ Site Program funded 185 grants:

Bladder, 47 grants, $5.3 million; Large Bowel, 57 grants, $5.3 million; Pancreatic, 33 grants, $2.1 million; Prostatic, 48 grants, $4.6 million.

Working cadre chairmen are:

Bladder—Gilbert Friedell, chief of pathology at St. Vincent Hospital, Worcester, Mass.

Large Bowel—Marvin Romsdahl, professor of surgery, M.D. Anderson Hospital & Tumor Institute, Houston.

Pancreatic—Isidore Cohn, chairman of the depart-

ment of surgery, Louisiana State Univ. School of Medicine, New Orleans.

Prostatic–Gerald Murphy, director, Roswell Park Memorial Institute, Buffalo.

CANCER CONTROL REPS DISCUSS ISSUES OF THE 80s AT AACI-RPMI MEETING

The two-day meeting on "Progress in Cancer Control" sponsored by the Assn. of American Cancer Institutes and Roswell Park Memorial Institute was attended by cancer control professionals representing 22 cancer centers, NCI, the International Union Against Cancer, the American Cancer Society, the American College of Surgeons Commission on Cancer and the Assn. of Community Cancer Centers.

Conference participants reviewed cancer control accomplishments of the programs in organizations represented. In workshops on the coordination of community services, professional outreach, reaching high risk populations, nursing and allied health interventions, and prevention, they discussed directions for future cancer control research and program development for the 80s.

Carlos Caban, program director for centers' outreach at NCI, reported that a number of policy, programmatic and administrative issues have surfaced in the cancer control program recently which demand resolution. These issues include: 1) redefinition of the centers outreach program, 2) establishing of eligibility requirements for participating centers, 3) defining the types of grants that will be funded, 4) establishing some limitation on the size of the outreach grants, and 5) determining means for peer review.

In summarizing the discussion, Curtis Mettlin, chairman of the conference, said that the meeting showed the cancer control community "has had significant impact in the fields of public health and on the lives of cancer patients and would continue to do so in the future." His view of the consensus of the meeting was that "because of their ability to bring together multidisciplinary efforts involving physicians, epidemiologists, behavioral scientists, nurses, planners and others, cancer centers were in a unique position to advance the mission of cancer control."

The conference was the first in which the centers' cancer control directors joined with the representatives of the community cancer centers' programs. Participants were in agreement on the importance of prevention, screening and detection, rehabilitation and continuing care, and of bringing modern cancer care technology to the patient as priorities for future program development.

Robert Thiessen, community oncologist in the Tacoma General Hospital program, described accomplishments there as unique and lamented that "there are still thousands of communities where every breast cancer patient receives a radical mastectomy and thousands of communities where a diagnosis of Hodgkin's disease is regarded as a terminal diagnosis."

While reporting on developing programs in their own settings, the community cancer center representatives were outspoken in their criticisms of NCI red tape and called for a de-emphasis of requirements for planning and evaluation in NCI supported programs. Rose Kushner, member of the National Cancer Advisory Board, defended NCI, reminding the audience that emphasis on program evaluation originates in Congress. Kushner's view was that it was the responsibility of cancer control workers in the field to develop the research and evaluation aspects of cancer control.

In keeping with that theme, the workshop reports emphasized opportunities for research on improved means of technology transfer, professional outreach, reaching high risk populations, community resource coordination, use of nonphysician professionals, and prevention. Joseph Cullen, UCLA, noted the significance of the emergence of organized prevention programs of such centers as Roswell Park, M.D. Anderson, and UCLA as means of studying and promoting the use of cancer detection procedures by the high risk population, and motivation and compliance behavior studies to enhance lifestyle change and smoking cessation.

Roswell Park will sponsor a workshop in September, 1981, on cancer communication and screening, with participation by AACI, ACCC, ACS, UICC, and perhaps others. Mettlin will be the chairman.

DCCP BOARD APPROVES NEW, RECOMPETING CONTRACTS WORTH $4.7 MILLION IN 1981

New contract supported projects and existing contracts being recompeted or renewed on a sole source basis, totaling more than $4.7 million in first year awards, have been given concept approval by the Div. of Cancer Cause & Prevention Board of Scientific Counselors.

RFPs for the contracts being competed will be issued by NCI's Research Contracts Branch over the next few months. All are planned for first year funding with 1981 fiscal year money.

Note: The figures listed as first year awards are estimates only. Proposals should be developed according to workscopes in the RFPs and should not rely on the dollar estimates in arriving at project costs.

New projects approved by the DCCP Board:

Expression of transforming genes in human tumors. Estimated first year award not to exceed $250,000 on a two year research contract. The DCCP staff narrative explaining the proposal:

In the past two-three years there has been a dramatic increase in knowledge of the transforming genes ("onc" genes) carried by retroviruses and of the gene products of some of them. These viral onc genes are believed derived by recombination from normal cellular genes. These cellular genes are highly conserved among all vertebrate species, and accordingly have been detected in normal human DNA. To date, about 8-10

distinct onc genes have been recognized, various ones of which have specificity for fibroblasts, B-lymphocytes, myeloblasts, and erythroblasts. Many of these have already been cloned in recombinant DNA host-vector systems, and others are in the process of being cloned. Consequently, it is now possible to prepare pure and well defined DNA probes inexpensively for all of these important genes. It therefore seems both feasible and highly appropriate that studies be carried out to determine if any of these genes are expressed in human tumors. This offers an unparalleled opportunity for basic molecular tumor virology to relate its progress to the problem of human cancer.

In general, the cloning and validation of the DNA of each onc gene is being accomplished in different laboratories. No single investigator has ready access to all of the DNA-probes, nor would many laboratories have access to a sufficient diversity of human tumors to permit a systamatic study of the expression of these genes in human cancer. It is proposed that NCI sponsor an R&D support effort to test all of the currently available cloned onc genes from the several contributing laboratories against appropriately extracted RNA obtained from a diverse set of human tumors. Currently available probes include those of Rous sarcoma virus, Moloney sarcoma virus, Kirsten sarcoma virus, Harvey sarcoma virus, Abelson virus, Snyder-Theilen feline virus, avian erythroblastosis virus, MC-29 avian virus, and avian myeloblastosis virus. In the initial phase of study a total of 100 tumors obtained from a variety of neoplastic conditions would be tested. Appropriate human tumor material can be made available from NCI resource efforts or already-extracted RNA from other similar specimens might be used.

It is recognized that this is an exploratory project, but the reagents are available and the contract will be well defined and limited. Positive results will not prove etiology; however, a systematic study might lead to new ways to characterize and classify human tumors as well as possibly providing tests for differential diagnosis.

This was proposed as a resource contract which would not require outside peer review. However, Board member Brian Henderson said, "I just think this is research. It will not be easy to do well, and I don't think it should be a contract." He suggested that it be supported through the grant mechanism.

Board member George Klein agreed that it was research, but suggested that those doing the work would need help in getting required material.

"I don't see why it can't be a contract," said Board member Louis Simonovitch. DCCP Acting Director Richard Adamson suggested it be changed to a research contract so that it would go through peer review, and the Board voted approval.

Hybridoma bank and distribution center. First year award not to exceed $225,000 on a three year resource contract. The narrative:

The hybridization of antibody-producing spleen or thymus cells with continuous plasma cell lines to yield hybridomas which secrete monoclonal antibodies is an important recent technological development. While hybridomas are still being primarily used in the field of immunology to study the diversity of cellular antigens, to probe antibody structure, and to study subpopulations of antibody-producing cells, the general use and development of hybridomas in cancer research is becoming more evident.

In the field of tumor virology, hybridomas are now being developed and used to explore host-virus relationships, virus identifications, structural-nonstructural viral proteins, and etiological assocations and mechanisms of carcinogenesis. Within the Biological Carcinogenesis extramural research program, a number of laboratories have already started to make use of this new technology. These studies involve investigations concerning RNA core tumor viruses, DNA viruses, and also multidisciplinary special projects. The scope of studies ranges from immunogenetic analysis of mouse leukemia viruses, to receptor protein study for gene regulation analysis, to the characterization of viral and viral-induced antigens in tumor cells.

A BCB-sponsored workshop on hybridoma technology was held in 1979. The objective was to develop directions for extramural research and technology that would help improve understanding of the role of viruses in human cancer and the mechanisms of carcinogenesis. The workshop included both formal and informal presentations by workers active in the field and topics discussed included the nature and specificities of hybridomas currently available, selection critieria for myeloma and spleen cells, immunization regimens, screening for characteristics of antibody produced, applications to tumor virus research, and mechanisms for central storage and distribution of hybridomas to the scientific community. The participants at the workshop strongly supported the establishment of a hybridoma cell bank and repository from which distributions could be made to the general scientific community.

In the proposed hybridoma bank, deposits of newly developed hybridomas will be made by the originating investigator after appropriate publication concerning its development and use. The cell hybrids will be characterized by the developing investigator for fusion partners, cloning information, culture media, specificity of reaction, quantitation of titer, and other important criteria. When the supply of donated materials is depleted, the bank will prepare additional quantities and send a special sample to the original donating investigator for verification and testing prior to any general distributions.

Resource for xenotransplantation and evaluation of human tissues and cells in athymic nude mice. Estimated first year award of $259,000 on a four year resource contract. The narrative:

Since (a) most of the information available on the mechanisms of chemical carcinogenesis has been obtained from studies conducted in rodent tissue systems and (b) most of the information on carcinogen effects in humans has been derived from the uncontrolled conditions of carcinogen exposure documented by epidemiological studies, the successful establishment and application of a model system for normal and neoplastic human tissue xenographs will aid the study of mechanism(s) of carcinogenesis in human epithelial cells and tissues.

This contract is an integral part of an ongoing collaborative study to develop model systems for studying carcinogenesis directly in human target tissues. The collaborative design involves (1) collection (surgery or immediate autopsy), (2) in vitro maintenance and treatment, and (3) xenotransplantation of normal, preneoplastic and neoplastic carcinogen treated and untreated human tissues in immunodeficient athymic nude mice. This contract will provide the continuation of the very vital third phase xenotransplantation segment of the study. A disease free athymic nude mouse colony, adequate to the needs of the program, has been established. In addition, methods have been developed that allow for long term survival of several human tissues (esophagus, bronchus, pancreatic duct, colon, prostate and mammary) as xenografts in nude mice for periods of greater than one year. These human tissues have maintained their viability and their histological integrity throughout these periods, which are adequate for the accomplishment of meaningful experimentation.

This project will serve as an essential resource for in vivo assay of (1) the transplantability of normal, premalignant and

malignant human tissues, (2) the effects of pretreatment in vitro with carcinogens and anticarcinogens on the growth patterns and tissue integrity of various human tissues as xenographs, and (3) the relationships between the level of DNA-adduct formation, malignant transformation and survival of human tissues in vivo as xenografts. Specifically, employing an essentially pyrogen free facility, (1) a stock colony of 600-900 athymic nude mice (Type I and II) will be bred and maintained on a continuing basis, (2) long term animal holding experiments using athymic nude mice will be housed for periods of up to two years, and (3) methods for the long term survival of xenotransplants of human tissues in nude mice will be employed and developed. Human tissues to be studied will include bronchus, pancreatic duct, colon, prostate, esophagus and mammary. Xenotransplanted human tissues will be frequently monitored in vivo for viability and the integrity of tissue specific characteristics, and, in some experiments, the xenotransplants will be treated with carcinogens in vivo.

Case control study of brain cancer and occupational factors. Estimated first year award of $150,000 on a three year support contract. The narrative:

Increased risk for adult cancer of the brain and central nervous system has been associated with exposure to occupational agents. An early indication of an association between brain cancer and occupation appeared in studies of workers exposed to vinyl chloride. A preliminary investigation of mortality among workers in the pharmaceutical industry conducted by the Environmental Epidemiology Branch of DCCP's Field Studies & Statistics Program showed an increased frequency of brain and CNS cancer among white males. Subsequently, clusters of brain cancer among workers in two oil refineries in Texas were identified by EEB, and further investigations are under way by EEB and NIOSH. In addition, two cohort mortality studies, one of Canadian workers and one of U.S. refinery workers, indicated an increased risk of these cancers.

The proposed study is an outgrowth of the EEB investigations of mortality among occupational groups. Observations from these studies, as well as suggestive results from other studies, need further evaluation and refinement through analytic investigations that will clarify the role of occupation while taking into consideration other factors. Reports of clusters of brain and central nervous system cancers among workers in several different types of refining and chemical plants, and the paucity of epidemiologic studies of this cancer site, underscore the need to implement a comprehensive study. A case control interview study is proposed because it will provide an opportunity to examine common exposures throughout many occupations, as well as to investigate the role of non-occupational factors (e.g., family history, drug exposures, etc.) in the origins of brain tumors.

Funds for this project have been requested from the NCI/-NIOSH Interagency Agreement. This will be a competitive project. An RFP will be issued after funds are approved.

The primary objective of the proposed study is to investigate etiologic factors for brain and central nervous system cancer among adult white males of the United States where the petroleum and chemical industries are heavily concentrated. A detailed protocol will be developed for a case control interview study of next of kin of about 1,200 adult males (600 cases, 600 controls). Cases will be drawn from death certificates from as many state vital records offices are necessary to achieve desired study size. Suitable controls will be matched to the cases by age, race, and case ascertainment source. Information regarding occupational and environmental exposures, family history, and other factors will be collected for all study participants. Next of kin interviews will be conducted for all cases and controls.

Henderson suggested that interviews with living patients might produce more information on classes of chemicals to which patients were exposed in their workplaces. "I don't see how the spouse would know the kinds of materials involved."

"The tumor and surgery frequently affect the patient's ability to respond," said Robert Hoover, chief of EEB's Environmental Studies Section. "We feel family members may be better sources."

The Board approved an occupational exposure study which had generated some controversy because NCI was willing to permit it to be funded by the industry being investigated. The Board's approval was conditioned on NCI assuming total control of the study and paying for it, at an estimated cost of $350,000.

The Formaldehyde Institute, a trade association, had agreed to undertake a study to evaluate the mortality experience of workers exposed to formaldehyde in industrial settings, with NCI's participation. The concern followed a report by the Chemical Institute of Toxicology of cancer of the nasal passages in rats exposed to formaldehyde which raised the possibility that the substance may be a human carcinogen.

Aaron Blair, DCCP project officer for the proposed study, told the Board that NCI had tentatively agreed to accept the Formaldehyde Institute's proposal for two reasons. "One is pragmatic. It would not be possible to do our own study for one or two years, and we feel it is urgent to start as soon as possible. The second is philosophical. It should be appropriate for industry to fund some occupational studies. The government and unions can't do it all."

Objections were raised by Irving Selikoff, director of the Environmental Sciences Laboratory at Mount Sinai School of Medicine, and Sheldon Samuels, director of Health, Safety & Environment for the AFL-CIO Industrial Union Dept. Both are members of the National Cancer Advisory Board.

Selikoff objected because, under the Formaldehyde Institute's proposal, participation in the cohort study by companies would be voluntary. "Since only self selected companies will be included, the investigation may be limited to the mortality experience of workers in plants with closed systems, with very little exposure." Those firms in which workers to be followed were exposed 10-15 years ago would not provide as valid information as would those in which workers were exposed 25-40 years ago, Selikoff said in a letter to Blair.

Samuels also objected to the voluntary aspects of the study. "Based on the half century of experience in government-industry cooperative studies in occupational health we are able to predict, with only slightly less certainty than the sunrise tomorrow, that the study will be skewed. Even if that does not actually occur, the forced intimacy in joint field efforts, selection of contractor, retrieval of data and analyses will destroy the credibility of the project on the basis

of appearance alone," Samuels wrote to Blair.

Siminovitch agreed that "there will be a perception problem when the results are announced." Board member Seymour Jablon commented, "If the Formaldehyde Institute says that formaldehyde is the most potent carcinogen known to man, there would be no problem with perception by the public. If it is marginal or negative, there will be a problem."

"If you want to fund this with NCI money, we'll fund it," Adamson said. "The issue will come up again, with industry funding some study."

Jablon asked if it would be possible for industry to give NCI the money for the study to be placed in escrow, with NCI awarding any contracts the study requires and paying for them from the escrow account.

"There is no reason to launder the money," Adamson said. "If we do it with industry money, we will do it in the open." Jablon responded that he did not mean the industry contribution would be hidden.

Siminovitch's motion that the study be funded by NCI and that it should not be considered a precedent was approved unanimously.

NCI has not determined yet whether the support contract required to assist the Field Studies & Statistics Program carry out the study will be competitive or sole source.

The Board approved a three year, noncompetitive support contract totaling an estimated $425,000 ($175,000 first year) for services required by FSS for a long term mortality study of workers in the furniture manufacturing industry. The sole source contract will go to Westat Inc. and will be funded under the NCI/NIOSH interagency agreement.

Contracts up for renewal and/or recompetition were brought to the Board for concept approval:

Resource for transplacental carcinogenesis studies in primates. Estimated first year award, $250,000 on a three year resource contract. The narrative:

Exposure to chemical agents during pregnancy may result in subsequent development of tumors in offspring, who may be several decimal orders of magnitude more susceptible to such agents than adults. Experiments in rodents indicate that both childhood malignancies and tumors of adult life, including carcinomas of living epithelia, can result from transient exposure to carcinogens during intrauterine life.

No experimental data existed on the significance for nonrodent species of transplacental exposure to carcinogens when a contract was established in 1973 to study this phenomenon in nonhuman primates. No government facilities were then or are now available for such a study. Since that time a contract supported colony of approximately 200 animals has been used to study the responses of embryonic, fetal, juvenile, and adult erythrocebus patas monkeys, and smaller numbers of rhesus and cebus monkeys, to the direct acting carcinogen ethylnitrosorea (ENU), the metabolism dependent carcinogen diethylnitrosamine, and (more recently) the tumor promoting agent phenobarbital.

Transplacental carcinogenesis has been demonstrated with ENU in both patas and rhesus monkeys. Two facts of great significance not demonstrable by rodent studies have emerged: the first trimester of pregnancy, rather than the third as in rodents, is the period of greatest fetal risk; the mothers are prone to choriocarcinoma induction and are perhaps at greater risk for other neoplasms than nonpregnant females. In transplacentally exposed offspring, to date, principally tumors similar to the pediatric neoplasms of man have appeared, following exposures similar to those used in rodent studies.

This contract will continue to provide maintenance, treatment, surgical manipulation, and necropsy of nonhuman primates. A limited number of animals will continue to be observed for the possible appearance of neoplasms like those of adulthood in man after prenatal exposure to carcinogens. The effects of systemic tumor promoting agents, so far documented only in rodents, will be studied, initially emphasizing hepatotropic agents because of the ease with which hepatocellular neoplasms can be recognized early by detection of serum alpha fetoprotein. In collaboration with other laboratories, comparative biochemical studies will be performed to investigate the pronounced differences in organ specificity for carcinogenesis by direct-acting chemical carcinogens in monkeys in comparison with rats and mice. The extraordinary resistance of one primate species (cebus appella) to carcinogenesis by ENU will also be studied biochemically, with emphasis on possible differences in capacity for biological processing and repair of damage to DNA.

Other DCCP existing contracts approved for recompetition will be described next week in ***The Cancer Letter.***

NCI CONTRACT AWARDS

Title: Large scale tissue culture virus production for cancer research
Contractor: Meloy Laboratories, $2,028,559.

Title: Cell proliferation and susceptibility to cancer of the large intestine
Contractor: Memorial Hospital for Cancer and Allied Diseases, New York, $200,581.

Title: Structure and distribution of integrated sequences of feline oncornaviruses, continuation
Contractor: Sloan Kettering Institute, $72,270.

Title: Studies of iatrogenic cancer and radiation dosimetry
Contractor: M.D. Anderson Hospital, $99,710.

Title: Familial cancer in melanoma patients
Contractor: M.D. Anderson Hospital, $95,852.

Title: Develop electrophoretic display cell
Contractor: Philips Laboratories Division, Briarcliff Manor, N.Y., $495,000.

Title: Breast Cancer Detection Demonstration Project
Contractor: Univ. of Southern California, $60,484.

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