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SCIENTIFIC COMMUNITY RALLIES TO SUPPORT DEVITA; IMMEDIATE SUSPENSION OF STRAUS' GRANT CONSIDERED

Scientists around the country, appalled by the ferocious attacks on Vincent DeVita by members of the Senate Committee on Labor & Human Resources, this week were rallying in support of the NCI director. Those who discussed the matter with ***The Cancer Letter*** expressed

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In Brief

CONGRESS SETS NCI RESCISION AT $10.785 MILLION; CENTERS TO BE FUNDED ACCORDING TO PRIORITY SCORES

CONGRESS COMPLETED action last week on the 1981 fiscal year rescision bill, compromising on $10.785 million as the reduction NCI must sustain from the original appropriation of $1 billion, 1 million. . . . **CANCER CENTER** core grants approved for payment by the National Cancer Advisory Board last month—and henceforth—will be funded on a sliding scale. The grant which received the highest priority score will be paid at or close to the recommended budget level, and the rest in descending order. Actual amounts will depend on amount of money in the centers core grant budget. William Terry, acting director of the Div. of Centers, Resources & Community Activities, told the division's Board of Scientific Counselors last week that money had been added for core grants to bring the total up to $70.6 million for FY 1981. The top priority score on this round was 137, the lowest 231. The linear payoff line will go from 137 to 215; those included will get the current level plus a percentage of the recommended increase. Those from 215 to 231 will receive either the current or recommended amount, whichever is lower. . . . **THE NEW** center core grant guidelines, hammered out with such difficulty over three and a half years, are now in effect. Applications for the next round, with the Oct. 1 deadline, will have to comply with the new guidelines. Center executives and members of the Cancer Center Support Grant Review Committee will be briefed on the new guidelines July 15. . . . **AGING CAN** have important effects on cancer chemotherapy in humans, NCI Director Vincent DeVita and National Institute on Aging Director Robert Butler wrote in a joint letter to cancer journal editors. Since many studies on effects of age use lab animals, DeVita and Butler asked editors to urge authors to include ages of animals in their manuscripts describing such research. . . . **ETHICS COMMISSION** staff draft report on various proposed systems for compensation of injured research subjects is available, and public comment is being solicited. For a copy of the report, write to President's Commission for the Study of Ethical Problems in Medicine & Biomedical & Behavioral Research, 2000 K St. N.W., Suite 555, Washington D.C. 20006.

ACCC URGES DEVITA REAPPOINTMENT, SAYS HE'S "IDEALLY SUITED" TO LEAD PROGRAM

(Continued from page 1)

disappointment over the direction taken in the hearing before the Senate committee, chaired by Orrin Hatch (R.-Utah). They were especially incensed over the unfairness of blaming DeVita for deficiencies in contract management practices which existed long before he became director of NCI and which, for the most part, have been corrected during his 18 months in that job.

They also feel that it was grossly unreasonable to lay the entire blame for the Marc Straus affair on DeVita's shoulders. The falsification of data in Eastern Cooperative Oncology Group studies at Boston Univ. surfaced in 1978, when Arthur Upton was NCI director. Upton decided that actions subsequently taken—firing of Straus by the university and expunging from ECOG records of data produced by Straus' group—were sufficient and did not press for an investigation. DeVita, as director of the Div. of Cancer Treatment, went as far as he could go when he took steps to prevent Straus from participating in any more clinical studies by forbidding his access to investigational drugs.

Most of the committee's ire was based on DeVita's decision not to inform the National Cancer Advisory Board about the charges when Straus' new grant application came before it. The new grant was for nonclinical research at New York Medical College where Straus was employed after leaving Boston. The allegations against Straus had not then been made public.

Committee members refused to accept DeVita's position that he felt it would not have been appropriate since the charges were unproven and no formal action had been undertaken. It is possible that Straus would have had legal recourse had his grant, with a very high priority score, been denied on the basis of unproven charges. No system was in effect which would provide for withholding grants until charges of misconduct could be probed.

The debarment system since put into place by NIH now will permit deferment of grant awards while allegations are being investigated.

The fact that NIH did not undertake an investigation of Straus until the Boston Globe series brought the charges into the open further aroused the committee's anger. Members also felt that DeVita at least should be attempting now to suspend the grant.

DeVita has been meeting with NIH officials since the hearing to determine what action can be taken immediately to suspend Straus' grant while the investigation is under way. Committee members feel that every dollar which goes to Straus now is money wasted and that doubt will exist about whatever findings he may report. A suspension probably would have to come from NIH, since it is NIH policies and regulations which are involved.

Many of DeVita's colleagues, within NIH and around the country, believe he is the best scientist administrator in the federal government. His scientific qualifications are unchallenged, and his outstanding administrative record as director of the Div. of Cancer Treatment was a major factor in his selection to be director of the Institute.

It seems apparent that the committee made such a big deal over the Straus matter because the case it had been trying to make during its four month investigation on NCI contracting practices had fallen flat. Hatch in his opening statement repeated the litany of deficiencies in contract operations reported by the Inspector General and General Accounting Office. Representatives of those agencies ran through them again in their testimony at the hearing.

Hatch was not in the hearing room when those representatives both stated that NCI had implemented most of the recommendations their agencies had made. Sen. Paula Hawkins (R.-Fla.), who was there, chose to ignore those statements and wound up the hearing by saying she was placing NCI on notice that it has 90 days to demonstrate improvements, and that she will call new hearings then if the situation warrants it.

Committee staff members, asked later for details on what would be expected of NCI in 90 days, responded only with "some movement to clean things up." In the context of the hearing, that could mean:

—Suspension of Straus' grant and completion of the NIH investigation.

—Progress in implementing a new community oncology program.

—Further evidence that deficiencies in contract management have been corrected.

—Initiation of efforts to collect the $1.1 million from Eppley Institute which GAO said was the amount paid by NCI for unauthorized work Eppley did in its carcinogenesis research contract. Committee members severely criticized DeVita for delaying action to recover that money.

DeVita responded that NCI first had been waiting for the Dept. of Justice to conclude its part in the case, as advised by legal counsel. Justice did pull out when the Grand Jury found that there was no evidence of criminal action. NCI then had to wait for the HHS legal office to produce certain documents, and was still waiting last week when the hearing was held. DeVita said he would insist that those documents be provided immediately.

The government might look a little silly in trying to get that money back. Former Eppley Director Philippe Shubik insists he had verbal authorization for the work from the project officer, Gio Gori. Shubik also points out that the work in question led to the discovery that vitamin C ameliorates the carcinogenic action of nitrosamines, a finding of pro-

found significance. That was only one of the products of the "unauthorized" research.

Sen. Howard Metzenbaum (D.-Ohio) was critical of leaks to the press by committee staff which resulted in publication of erroneous information on the Eppley Grand Jury action.

"I'm opposed to trying legal matters in the media," Metzenbaum said. "The Grand Jury acted in that matter and found there was no basis for a criminal case. It is not appropriate for Senate committee staffers to be arguing this case in public. We ought to respect legal proprieties."

Hatch responded that the committee was concerned with the civil action to correct the "$1.1 million ripoff of the taxpayers."

It was somewhat ironic that a few minutes later, Metzenbaum tore into DeVita on the Straus matter. "If you were in private business, you would not give a $900,000 contract to someone who had falsified data." The point DeVita had been trying to make was that it was not yet proven that Straus had falsified data. Metzenbaum appeared willing to abide by the philosophy of presumption of innocence in one case but not in the other.

Metzenbaum savaged DeVita, saying at one point, "The problem isn't with Dr. Straus, it is with you." He was gentleman enough to phone DeVita a couple of days later to apologize.

Hatch in his opening statement said he applauded the commitment of the National Cancer Act which has led to an appropriation of a billion dollars a year for NCI. Congress does not "agonize over these appropriations. We are heartened by past successes. We are grateful for the contributions of those dedicated and gifted men and women who have made careers of this fight, often foregoing larger financial rewards in the process. The committee it seems to me has approached this inquiry in a spirit of strict neutrality, devoid of any preconceptions of guilt or innocence. There is no desire or attempt here to dictate the terms of scientific inquiry. Nor is there any desire to cut the budget of a worthy enterprise or to hold the cancer research effort hostage to any political considerations. Rather, we are attempting to find out how efficiently a publicly funded research organization is spending a billion dollars a year of the public's money "

Hatch, 47, is in the last two years of his first term in the Senate. A devout member of the Church of Jesus Christ of Latter-day Saints, he obtained a JD degree from the Univ. of Pittsburgh after graduating from Brigham Young Univ. His colleagues in general consider him a man of integrity and an effective senator, and if he wins reelection next year, he could be a powerful figure on the national scene for many years, perhaps even a White House contender.

The tinge of McCarthyism which came out of the hearing, in which a superbly qualified person was pictured as less than competent on the basis of irrelevant and outdated information, is not worthy of a man of Hatch's reputation and prospects.

Other charges which came up in the hearing were even less relevant to DeVita's managerial capabilities. The most serious was another case of data falsification at Massachusetts General Hospital in 1979. John Long, the principal investigator on an NCI grant, admitted altering data for articles submitted to scientific journals and resigned his job. Hatch was critical because NCI did not punish Long and allowed the grant to continue. DeVita said that the grant was terminated, other than an amount required to establish the falsification. The only thing left to do would be to prosecute, and the Dept. of Justice refused to do so, DeVita said.

Several relatively minor conflict of interest charges were brought up at the hearing:

- Franco Muggia, who was director of the Cancer Therapy Evaluation Program in DCT until he left about two years ago for a position at New York Univ., while at NCI helped develop a contract supported clinical trials program in gastrointestinal cancer. After moving to NYU, Hatch said, Muggia was involved in an effort to get one of those contracts for the university. The effort was not successful; had it been, it probably would have been a violation of the federal law which forbids former government employees from participating in government financed activities which they had helped establish while in government.

- Gregory O'Conor, director of NCI's Office of International Affairs, had participated in award of a contract with the International Union Against Cancer (UICC) while serving as a member of the UICC Board of Trustees. DeVita said O'Conor had not been aware this represented a conflict of interest and that he immediately resigned from the UICC Board when it was called to his attention.

Hatch said that "Dr. O'Conor wrote to Mr. [James] Graalman [chief of NCI's Research Contracts Branch] urging award of the contract to UICC, while he was a member of the Board. That is a criminal violation. I'm not suggesting that a fine or imprisonment are in order, but at least a reprimand."

"I agree that persons in high positions at NCI should avoid conflicts of interest," DeVita said. "In this case, there was no personal gain for Dr. O'Conor."

- Nicholas Day, an Australian citizen, was hired by NCI on a short term basis to help develop a contract program to study problems with radiotherapy for cervical cancer. NCI intended to award the contract to the International Agency for Cancer Research, until DeVita learned that IARC planned to hire Day to help conduct the study. DeVita told IARC that it could not have the contract if Day par-

ticipated in it, and IARC responded that it probably would not accept the contract in that case.

Hatch brought up DeVita's travel expenses, one of the charges leaked to the press before the hearing by committee staff. "Last year, your own travel cost $10,200," Hatch said.

"My own travel last year was $4,000," DeVita said. "The entire amount for travel since I have been director is $7,800."

To put that figure in perspective, Arthur Upton's travel cost in one year was $27,000, the largest part of which was incurred in meeting NCI's international obligations. If DeVita is to be criticized over travel, it might be more appropriate to criticize for not traveling enough.

The leak on travel costs included the information that DeVita did not pay his own way to Paris when he picked up the $41,000 Griffuel Prize. At least one newspaper, in an editorial based on the leaked story, blasted DeVita for billing the government for his expenses. The fact is that the French volunteer cancer research organization which made the award picked up DeVita's hotel expenses. It has been a long established practice at NIH that when one of its employees receives a prestigious award, NIH will pay the travel expenses—including those going to Stockholm to pick up a $200,000 Nobel Prize.

The Assn. of Community Cancer Centers expressed strong support for DeVita in a letter sent by President Herbert Kerman to major newspapers and to each member of the authorizing and two appropriations committees in Congress.

"The recent hearings of the Senate Committee on Labor & Human Resources, chaired by Sen. Orrin Hatch, and its Subcommittee on Investigations & General Oversight, chaired by Sen. Paula Hawkins, reviewed various administrative aspects of the National Cancer Program," Kerman wrote. "Purpose of the hearings was cited by Sen. Hawkins in her opening statement: 'To assist and support this vital program in reaching a goal so important to all human kind—the conquest of cancer.'

"We applaud this purpose and know that a clear signal has been given to the leadership of NCI to continue their reassessment of the Institute's administrative policies. To accomplish this stated goal of the committee, it is suggested that the committee immediately and strongly support the [reappointment] of Dr. Vincent T. DeVita."

Kerman said that DeVita's uncertain status has "impeded" his efforts to assemble staff, make administrative changes, and develop future directions.

"As practicing physicians representing a constituency of the nation's community cancer physicians (the overwhelming majority of whom receive no funds from the Cancer Institute), we recognize Dr. DeVita as a brilliant clinician and a dedicated medical scientist with significant administrative skill. He has the confidence of the biomedical community and is ideally suited to respond to the recommendations and concerns of the Committee and to continue to lead the nation's crusade against cancer. Indeed, it should be noted that many of the administrative concerns recognized by the Committee and Subcommittee were first noted by the GAO and IG reports which were developed while the Institute was under other leadership. It is our impression that Dr. DeVita has made substantial progress in correcting many of these administrative deficiencies.

"This combination of administrative and scientific competence, along with the ability to inspire confidence and provide leadership to a diverse scientific community, is a rare find," Kerman concluded.

CARCINOGENESIS, EPIDEMIOLOGY, SMOKING RFAs GET DCCP BOARD CONCEPT APPROVAL

Three new RFAs (request for applications for research grants) received concept approval from the Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention in chemical carcinogenesis, epidemiology and smoking and health. An estimated total of $3.25 million will be earmarked to fund the grants in their first year, if enough high quality applications compete successfully.

The proposals will be developed by DCCP staff into formal RFAs which will be published within a few months. The specific proposals and staff description of the projects follow:

Role of tumor promoters, hormones, and other cofactors in human cancer causation. Estimated first year cost, $2.5 million to fund several grants, probably for awards of four years. The narrative:

Experimental tumor promotion, originally demonstrated in mouse skin, has been analogously modeled in organs of laboratory animals, notably the liver, and in cell culture. It has been widely postulated that the phenomenon of tumor promotion may also apply to people and may constitute an important consideration relative to the occurrence of cancer in humans.

The intent of the proposed RFA would be to encourage research which might help to define the role of tumor promoters, hormones and other cofactors in human cancer causation. The focus would be on nonphorbol tumor promoters, hormones and cocarcinogens.

The following representative research is projected: (1) development of nonphorbol tumor promotion models and of cocarcinogenesis models in experimental animals, with respect to organs which are at high risk for cancer in people; (2) development of nonphorbol tumor promotion models and of cocarcinogenesis models in human and in nonhuman culture systems; (3) identification of nonphorbol tumor promoters and of cocarcinogens present in the human environment; (4) studies on mechanisms of action of nonphorbol tumor promoters and of cocarcinogens present in the human environment; (5) dose-response studies on nonphorbol promoters in experimental animals; (6) studies to test the possibility that hormones may serve as a tumor promoter or other cofactor role in carcinogenesis in experimental animals; (7) studies to test the existence of a tumor promotion role/involvement with respect to the following: bile acids, saturated/unsaturated dietary fat, alcohol abuse, salt abuse, and free oxygen radicals; and (8) interdisciplinary studies involving epidemiologists and

experimentalists to test hypotheses on tumor promoters generated by either.

The RFA would specify that: (a) the chemical carcinogens used in these studies should be chosen from among those which are organic compounds, are present in the human environment, and are known to be carcinogenic for humans or for experimental animals, or for both; (b) the choice of co-carcinogen(s) and of nonphorbol tumor promoters should be from among those present in the human environment, and (c) the experimental animal(s) used should be representative of those commonly employed in carcinogenesis research.

Epidemiologic studies of rare tumors. Estimated first year cost, $400,000, probably eight grants at $50,000 each in two year awards. The narrative:

Epidemiologic investigations tend to emphasize more prevalent forms of cancer. In the western world these would include cancers of the lung, breast, prostate, colon-rectum, stomach and bladder.

There is a number of tumors, occurring less frequently in the US that have not been emphasized as the focus of studies. Among these lesser studied tumors are thyroid carcinoma; soft tissue sarcoma; salivary gland tumors (malignant); adenocarcinoma and adenosquamous cancer of the cervix; cancer of the penis; chronic myelogenous leukemia (CML); adult bone and joint cancers (osteosarcoma, fibrosarcoma); male breast cancer; Kaposi's sarcoma; tumor of the small bowel (by histologic type); multiple myeloma and acute lymphocytic leukemia (ALL) in adults.

Studies of distribution in time and space are necessary to provide clues of association and to generate causative/etiologic hypotheses. Such working hypotheses can then be examined in more analytic (case/control or cohort) studies designed to provide information on etiology and natural history of a particular cancer, as well as the possibility of providing studies of better insight into more common tumors.

It is anticipated that subsequent case/control or cohort studies of less common tumors developed following descriptive studies could compete in the traditional investigator-initiated research grant program.

The pharmacologic role of nicotine in diseases related to tobacco products. Estimated first year cost, $350,000 for three year awards. The narrative:

Past studies have shown nicotine to be the only controlled variable in tar which is consistently related to the rate of tumor incidence in test animals. However, in separate studies, nicotine itself proved not to be a carcinogen. It has been noted that the relationship between carcinogenic activity of smoke condensates and their nicotine contents may be caused in part by the conversion of nicotine to tobacco-specific nitrosamines or to the co-occurrence of nicotine and some other unidentified carcinogen. Tobacco products made from the lamina of plants grown on high levels of nitrate fertilizer contain higher levels of nicotine and following combustion show higher levels of volatile nitrosames. The exact role of nicotine, its metabolic and pyrolytic products associated with inhalation must be clarified in relation to diseases associated with smoking. Such information is essential in order to evaluate health effects from various tar/nicotine ratios in cigarettes currently smoked.

DCCP BOARD REVIEWS CONCEPTS FOR NEW, RECOMPETED CONTRACT PROPOSALS

The DCCP Board of Scientific Counselors also acted on a massive number of concept reviews for proposed new contract supported resource and research projects, recompetition of existing contracts, and a variety of noncompetitive contract renewals.

DCCP Acting Director Richard Adamson said that an effort was being made to obtain concept approval for up to a year and a half ahead of time.

Those projects for which the Board approved the concept will be developed into RFPs, availability of which will be announced as they are ready for distribution.

The Board's action on competitive contract proposals follows.

Support services for a mortality study among workers exposed to formaldehyde. Estimated first year award, $200,000 with total project estimate over three years, $500,000. The narrative:

Formaldehyde is widely used in industrial operations. Human exposure is known to cause such acute effects as eye, nose, throat, and skin irritation. Although chronic effects have not been well documented, the recent report by the Chemical Industry Institute of Toxicology of cancer of the nasal passages among rats exposed to formaldehyde vapor raises the possibility that this substance may be a human carcinogen. To assess the potential for a mortality study of workers exposed to formaldehyde, a collaborative project involving NCI and Formaldehyde Institute was launched to locate suitable populations of workers for study and to secure cooperation of individual companies (phase I). Phase II was to include the actual assembling of the study cohort, evaluating exposures, and determining mortality.

The protocol for the entire study (phases I and II) was reviewed by the DCCP Board of Scientific Counselors at the September 1980 meeting. The Board moved that the phase I continue as designed, but that NCI fund phase II of the study. The Board further recommended that an advisory panel be assembled to provide advice to NCI investigators regarding various aspects of the study. An advisory panel, chaired by Dr. Brian Henderson and including Dr. Jennifer Kelsey has been organized and met with NCI staff in early May to review data collected during phase I. The number of workers to be included in phase II cannot be determined at this time; however, it appears that a cohort of 5,000-10,000 workers from formaldehyde producing, resin making, textile, plastic, and film coating industries having contact with formaldehyde before 1966 can be assembled.

A cohort of persons having contact with formaldehyde at their place of work will be assembled to determine whether such exposure may be carcinogenic among humans. If a cancer risk is evident, effects of level and duration of exposure will also be evaluated to establish dose related patterns Summary, as well as age, race, and sex-specific mortality rates for various causes of death among persons having contact with formaldehyde at their place of work, will be compared to rates from the US general population. The cohort will be developed from records of formaldehyde producing or using companies. All persons in the cohort will be traced to determine their current vital status. Death certificates will be obtained for those deceased and coded to determine underlying and contributing causes of death. Job titles, work locations, and available workplace measurements will be used to develop estimates of formaldehyde exposure among the study participants. The date of first employment and years of employment will be used to establish the timing and duration of exposure.

Although this is a collaborative study between NCI and the Formaldehyde Institute, NCI investigators will take the lead in all aspects of the study.

Mortality among airplane maintenance workers. Estimated cost, $225,000 a year for three years, which will be funded through NCI by the Air Force. The narrative:

In the past, workers engaged in the servicing and mainte-

nance of military aircraft have been exposed to a wide variety of solvents and other chemicals. Workers at Hill Air Force Base, Ogden, Utah, have had putative exposure to chloroform, trichloroethylene, zinc chromate and other potentially hazardous substances. Concerns of the American Federation of Government Employees regarding these exposures prompted a preliminary study of this population, which suggested the possibility of an excess of neoplasms of the lymphatic and hematopoietic system. Because of public concern, Senators Kennedy and Hatch have encouraged the Air Force to fund an epidemiologic study. A feasibility study, now under way, indicates that employment records from 1952 to the present are essentially complete and of high quality. The Committee on Toxicology, National Research Council, after reviewing material on Hill Air Force Base, suggested that a two phase study design be used; a historical cohort mortality study to be followed by a case-control study of any cause of death shown to be in excess.

Objectives will be to compare the mortality experience of exposed workers at Hill Air Force Base with internal and external control groups, and for causes of death found in excess, determine associations with particular jobs or exposures.

The cohort will consist of 15,000-20,000 civilian employees at the base aircraft maintenance facility during 1952-1957. The cohort will be assembled from records at the civilian branch of the National Personnel Records Center from the individual earnings record which includes name, date of birth, and Social Security number.

Occupational exposures experienced by the cohort members will be estimated using (a) job titles and organizational symbols, (b) directories of organizational and functional codes, (c) where possible, position descriptions and technical orders. The date of first employment and years of employment in exposed jobs will be used to estimate indices of exposure.

Mortality patterns among the exposed members of the cohort after appropriate adjustments for age, race, sex, and time of death will be compared with mortality patterns among (a) non-exposed coworkers as internal controls, (b) residents of Utah, and (c) the US population. If any causes of death are found to be in excess, as well as for selected causes of death, case-control studies will be used to further investigate potential associations using complete work histories and other information as available.

Cancer following tonsil irradiation/physical examinations and blood studies. Estimated cost $90,000 first year, total of $150,000 over two years. This project will be offered in a sources sought announcement to "test the market" and determine if there are more than one potential contractors. Otherwise, the contract will be awarded to Brigham and Women's Hospital in Boston on a sole source basis. The narrative:

Individuals who received treatments for benign conditions of the head and neck as children have been shown to be at risk for developing thyroid cancer later in life. To date, however, the actual increase in thyroid cancer due to head and neck irradiation has not been accurately determined with estimates ranging between less than 1 and 8 percent. This variation may be due to differences in the radiation doses that were received but is more likely due to some risk estimates only being based on results from screening examinations of exposed individuals who were part of a recall program. In these studies, the risk of radiation induced thyroid disease could not be properly assessed because the incidence in a nonexposed group was not obtained, and because the significance of small, "occult" cancers only detected at screening is still unknown. Some studies have also reported radiation induced thyroid nodular disease to be in excess of 30 percent.

It is thus important to accurately estimate the risk of thyroid disease due to head and neck irradiation and to factor out the proportion of the risk that is related to screening only radiation exposed individuals. Over the past two years, the Environmental Epidemiology Branch of NCI, in collaboration with the Children's Hospital Medical Center in Boston, has been conducting a followup study of children who were treated between 1938-1969 for lymphoid hyperplasia (primarily enlarged tonsils and adenoids) either by radiation or surgery. Approximately 1,650 radiation exposed individuals with available dosimetry records, and 1,650 nonexposed individuals (those who had surgery only) are being located and sent questionnaires regarding health status. The objective of the questionnaire phase of the study is to evaluate the late effects of head and neck irradiation in childhood (i.e., thyroid disorders, and cancer) and to quantify any effects in terms of radiation dose, age at exposure, latent period, and sex.

Since nodular disease is relatively "benign," some individuals may not know they have the disease, and the results of the questionnaire will probably yield an underestimate of the true incidence. The objectives of the proposed physical examination are to more accurately determine the risk of thyroid nodular disease, and to adjust for the potential detection bias of only screening radiation exposed persons.

Approximately 1,500 physical examinations will be conducted to detect thyroid nodules and head and neck cancers in exposed and nonexposed individuals. A unique feature of this study is the excellent comparison group; i.e., individuals who had tonsillectomies instead of radiotherapy, who will receive the same screening procedures as the exposed group. The Human Investigations Committees at both the Children's Hospital Medical Center and the Brigham and Women's Hospital have approved the study protocol. Physicians will follow the guidelines outlined in the government publication "Information for physicians: Irradiation-related thyroid cancer" (NIH 77-1120). Blood samples will be taken from the study subjects and serum calcium levels will be determined (recent case reports have indicated an association between head and neck irradiation and the development of parathyroid nodules). Plasma thyroglobulin concentrations will also be determined since high levels may be a predictor of thyroid cancer risk. The results of the physical exam and blood determinations will be sent to researchers at EEB for analysis.

Support services for a study of cancer following radioactive iodine therapy for hyperthyroidism (in collaboration with the FDA Bureau of Radiological Health). Estimated first year cost $300,000, total $900,000 over three years. Multiple awards will be made. The narrative:

Ionizing radiation is widely known to be carcinogenic. However, the issue and nature of radioactive iodine (131-I) carcinogenesis remains unresolved. 131-I is used widely in both medical therapy and diagnosis and is the primary release product from nuclear power generation. Several previous studies have addressed the problem of the carcinogenic effects of 131-I exposure but due to the limitations of these studies (small numbers of patients and too short of followup), many questions remain unanswered. A more definitive evaluation of the effects of 131-I exposure is needed as over 200,000 patients are exposed each year to medical 131-I.

In 1964, the Bureau of Radiological Health initiated the National Thyrotoxicosis Therapy Followup Study (TT Study) in an attempt to evaluate the risk of cancer following 131-I therapy for hyperthyroidism. These patients were treated in 26 different clinics between 1948-1964. The cancer incidence after treatment in 23,000 patients treated with 131-I was compared with that in 14,000 patients treated surgically or with drugs. This study ended in 1968. No difference in post-treatment leukemia incidence was observed between the study groups. However, the mean followup time for patients treated with 131-I was less than eight years, which is too short a time to evaluate the risk of cancer following 131-I therapy. Previ-

ous studies have shown that the latent period for radiation associated cancer (excluding leukemia) is much longer.

In 1977, a feasibility study was conducted at one of the original participating clinics in the TT Study (Mayo Clinic) to determine if a second survey of the entire group was possible. Followup in this study was 93 percent complete and the findings suggested increased risks of thyroid cancer and organs of high 131-I exposure. The present study proposed to resurvey part of the original TT Study population in order to evaluate the risk of cancer following 131-I therapy. This second survey will add 10-15 years of followup, The advantages of studying this population include: the information on treatment has already been abstracted and only additional patient followup is proposed; the doses from 131-I therapy vary widely, allowing evaluation of dose response relationships; and the number of patients exposed to 131-I is large and radiation dosimetry is complete.

Objective of this study is to conduct a second survey of patients treated for hyperthyroidism (originally enrolled in the TT Study) in order to evaluate the carcinogenic effects of 131-I exposure. Support services are required to followup former patients, abstract additional medical histories, obtain death certificates, mail questionnaires and prepare edited data tapes.

Proposed methodology is a retrospective cohort study. A second survey of hyperthyroid patients in the largest clinical centers as this is the most cost effective approach. Of the original 26 centers in the TT Study, 12 are found in three cities (New York, Boston, and Los Angeles). The numbers of patients in these clinics (23,000) account for 61 percent of the entire TT Study population. The contractor will locate the surviving patients in these clinics and obtain information on vital status (and cause of death) and malignancies through mail questionnaires or collection of death certificates. For reported cancers, copies of pathology reports and hospital discharge summaries will be obtained. Data will be analyzed using standard methods for prospective studies including life tables and multivariate analysis. The incidence of cancer by radiation dose will be analyzed.

Followup study of women evaluated for infertility. Estimated cost, $98,000 for a one year contract. This will also be offered first in a sources sought announcement to test the market. If other sources are not found, it will be awarded to the Mayo Clinic. The narrative:

Nulliparous women and women with a late first pregnancy are at an increased risk of developing neoplasms of the breast, endometrium and ovary. Possible explanations are that either a change in the hormonal milieu occurs consequent to first pregnancy or that abnormal profiles are associated with absolute or relative infertility. Studying a cohort of women treated for infertility will allow us to compare disease incidence among subgroups with differing abnormalities, and may aid us in understanding the mechanisms of carcinogenesis. If an abnormal hormonal milieu is the important factor in contributing to an excess cancer risk those women with specific identifiable hormonal problems will be of particular interest. The proposed study will allow evaluation of an hypothesis regarding breast cancer etiology that has received recent interest. This hypothesis proposes that women who exhibit luteal phase defects may be at increased risk due to their relatively unopposed state of endogenous estrogens. The only followup study of infertile women that has been conducted found tentative support for this hypothesis, since excess mortality risks from all causes and from breast cancer were found for women with a progesterone deficiency. However, this study was severely limited by the number of study subjects and by the length of followup. The present study will allow further evaluation of this issue and will also allow examination of various infertility treatment effects. Of particular interest will be radiation exposures to the pituitary and/or ovaries and use of progestational agents.

Proposed methodology is a retrospective cohort study. Approximately 2,500 women evaluated for infertility during a 30 year period (1935-1955) will be followed to the present time for subsequent disease risk. Medical records will be abstracted to obtain the following information: demographic characteristics, menstrual and reproductive history, the diagnostic workup for infertility and detailed infertility treatment details. Followup details on subsequent reproductive events, development of malignancies and vital status (including cause of death) will be sought through personal contact and through a population based tumor registry. Data will be analyzed using standard methods for prospective studies, using internal comparison (e.g., comparing rates for those with and without a progesterone deficiency) and external comparisons.

It is necessary that this study be conducted in a setting where large numbers of women have been treated over an extended period of time and where there is sufficient followup. It would be useful if this information could be related to the representative experience of an identifiable population in order to minimize the possibility of referral bias. Finally, in order to evaluate specific hypotheses relating to endogenous hormonal states, the diagnostic workups for infertility should be detailed and be supported by appropriate laboratory tests.

NCI CONTRACT AWARDS

Title: Adjuvant chemotherapy trial in head and neck squamous carcinoma, continuations

Contractors: American College of Radiology, $308,059; Univ. of Cincinnati, $83,640; Univ. of Maryland (Baltimore), $36,573; Memorial Hospital for Cancer & Allied Diseases, New York, $59,325; Univ. of Michigan, $67,958; Northern California Cancer Program, $59,754; and Univ. of South Florida, $140,520.

Title: Evaluation of ultrasonic contrast agents gelatin encapsulated microbubbles

Contractor: Stanford Univ., $433,152.

Title: Suppression of endocrine function by systemic agents as treatment of human breast cancer, continuation

Contractor: Pennsylvania State Univ., Milton S. Hershey Medical Center, $71,899.

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.

RFP NCI-CM-17364-29

Title: *Master agreements for preclinical pharmacology task orders*

Deadline: *Approximately Aug. 1*

The Developmental Therapeutics Program, Div. of

Cancer Treatment of NCI wishes to establish task order contracts with organizations having the capability to conduct preclinical pharmacologic studies on a variety of new antitumor agents of potential clinical interest. Task order contracts are master agreements competitively negotiated and awarded to more than one contractor. These contracts are designed to accomplish a specific task as promptly as possible.

The objectives of the task order contracts will be: 1) The complete pharmacologic workup, in mouse and dog, of the drug under study including absorption, distribution, metabolism, excretion and pharmacokinetics (ADMEP). This study will be conducted in two phases. The first phase will consist of development of appropriate assay methodology to measure anticipated tissue levels of the drug based on the probable dose level to be used. If the first phase if successful, the second phase of the study will address the ADMEP using the assay developed.

2) The conduct of a narrow pharmacologic study which will address the special pharmacologic properties of a particular antitumor agent. These studies may include but are not limited to (a) chemical structural determinations of metabolites; (b) bioavailability studies; (c) enzymology; (d) autoradiography, and such other narrowly defined studies as may be needed.

3) Investigate the effects of coadministration of other drugs on the basic pharmacologic profile of the drug of interest.

To meet these needs, DTP is seeking organizations with the facility to perform a variety of pharmacologic studies with an appropriate skillmix that would permit them to satisfactorily complete the requested studies.

Multiple master agreement awards are anticipated under this project. Master agreements will be awarded, against which individual task orders will be awarded on a completion of level of effort basis as determined by the contracting officer.

Contracting Officer: Clyde Williams
RCB Blair Bldg Rm 228
301-427-8737

RFP NCI-CP-FS-11009-65

Title: *Environmental cancer utilizing pre-paid health plans*

Deadline: *July 15*

The Div. of Cancer Cause & Prevention of NCI, Environmental Epidemiology Branch, has a need to evaluate rapidly hypotheses concerning the environmental causes of cancer. A rapid and relatively inexpensive way to accomplish this for various environmental exposures is by utilizing already recorded information from a pre-paid health plan (PPHP) on large groups of patients with a particular cancer, and on a comparable series of persons without the disease. Because of the nature of PPHP records, the primary hypotheses that can be tested involve those associated with the use of therapeutic drugs, medical irradiation, clinical conditions, surgical procedures, occupation, location of residence, and exposures that are highly correlated with one of these variables.

Utilizing longitudinally recorded information concerning demographic and specific exposure characteristics of cases and controls, representative of the group from which the cases are drawn, is a valuable way to test hypotheses rapidly and to determine whether more extensive study is required.

The duration of this contract is expected to be three years, targeted for award in September 1981. There are no specific geographic requirements for the location of the contractor. It is assumed that the contractor will be the organization under which the prepaid health plan is administered.

Respondent must (1) have at least 20 years of experience in providing outpatient and inpatient medical services for a defined population; (2) have a prepaid health plan base in excess of over 150,000 individuals annually, averaged over the last 15 years; (3) have the capability of identifying all cases, or a representative sample of all cases that have occurred in this population over the last 10 years; (4) have a computerized system for the health plan population which would allow an unbiased selection of comparison individuals, matched to the cancer cases on the basis of age, sex, date of health plan entry, and presence within the plan at a specified date; (5) have provided the inpatient and outpatient medical services for the base population and have readily identifiable the complete inpatient and outpatient records, and the capability of assembling these records in an efficient manner; (6) have extensive experience in designing abstract forms and have used them to collect data from their own records; (7) have experience in computerization and computer editing of large data files; and (8) have research experience in utilizing a particular PPHP's records in the conduct of cancer research, and interest and experience in etiologic research.

Contract Specialist: Eileen Webster
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301-427-8888

The Cancer Letter _Editor Jerry D. Boyd

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