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IT'S OFFICIAL: HOUSE APPROPRIATIONS COMMITTEE GIVES NCI $81 MILLION INCREASE OVER PRESIDENT'S REQUEST

The House Appropriations Committee came through, as tentatively reported last week (The Cancer Letter, Sept. 16), with an $81 million increase for NCI over the President's FY 1984 budget request. The committee stipulated that the increased funds would:

* Restore $19.8 million cut from the cancer centers assuring that money will be available to fund the 20 core grants which will be up for renewal during the fiscal

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In Brief

GEORGE VANDE WOUDE OF NCI NAMED PI FOR LITTON BIONETICS BASIC RESEARCH CONTRACT AT FREDERICK

GEORGE VANDE WOUDE, chief of the Laboratory of Molecular Oncology in NCI's Div. of Cancer Cause & Prevention, has been selected as the permanent director of the Litton Bionetics Inc. basic research program at the Frederick Cancer Research Facility and principal investigator of LBI's contract with NCI for that operation. Vande Woude assumed his new position Sept. 19. James Liverman has been serving as acting PI of the contract. Michael Hanna formerly headed all of Litton's operations at FCRF, before the contract was split into five new contracts last year. Hanna declined to remain as head of the reduced operation and left to start a new research institute for Litton. NCI's award of the new contract to Litton included the stipulation that NCI would have to approve the new PI. Takis Papas was named acting chief of the Laboratory of Molecular Oncology by DCCP Director Richard Adamson. . . . ROBERT HOOVER, who has been acting chief of DCCP's Environmental Epidemiology Branch, has been appointed permanent chief of the branch. . . . DAVID LONGFELLOW is acting chief of the Chemical & Physical Carcinogenesis Branch in DCCP's Extramural Program, taking over after the retirement during the summer of Thaddeus Domanski. . . . JAMES DUFF, who has been chief of DCCP's extramural Biological Carcinogenesis Branch, has retired. Jack Gruber is serving as acting chief. . . . NCI WINNERS of the NIH Director's Awards: John Driscoll, acting director of the Developmental Therapeutics Program; Brian Kimes, chief of the Cancer Biology Branch; and Mark Kochevar, administrative officer of the Clinical Oncology Program.

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HOUSE COMMITTEE RESTORES FUNDS CUT FROM CENTERS, RECOMMENDED LEVELS

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year (or, if any new centers compete successfully, fund a combination of 20 renewals and new grants). The Administration had slashed the centers budget to help pay for NCI's full complement of 817 competing grants, the Institute's share of NIH's obligation of 5,000 competing grants. The cuts would have enabled NCI to fund only four competing center core grants, although Director Vincent DeVita has insisted additional money would have been found somewhere to support most of those grants. He'll be spared that exercise now, or will if the full House and the Senate concurs.

* Restore $35 million for research grant direct costs, with a stipulation that grants be funded far closer to the levels recommended by study sections than had been projected in the Administration's budget. The committee noted that the budget request was based on an NIH average of a six percent reduction from recommended levels for noncompeting grants and 11.3 percent reduction for competing grants. The committee report calls for payment of 96 percent of recommended levels for competing grants and for "approximately" full recommended levels for noncompeting grants. "The committee does not agree with a policy which inflates the number of projects supported by underfunding each project," the report said.

* Restore $16.8 million for payment of full indirect costs. The report noted that HHS is conducting a study of the problem of escalating indirect costs. "The committee feels strongly that the full indirect costs of research should be reimbursed to the institutions at which it is conducted but is concerned about the rate at which these costs are escalating and it is not convinced that the present system for calculating these costs is equitable or sufficiently uniform to be fair to all institutions," the report said. The committee asked that a government wide plan be developed for calculating indirect costs on research supported by agencies with R&D grants. "Meanwhile, the committee has added $77 million to the NIH appropriations to enable NIH to pay the full indirect costs of its research grants."

* Add $2 million for cancer clinical education, which had already been increased in the President's budget by $2 million, to $8 million. The committee's earmark would bring the total to $10 million.

* Add $7.3 million for R&D contracts. The report does not spell out where the additional money should go. That would appear to give NCI some flexibility, with drug development and various intramural programs the probable beneficiaries.

* Add $317,000 for research career awards, bringing that total to nearly $6 million.

Those earmarks total less than $74 million, which would give NCI about $7 million of unallocated (for the moment) money. Lifting the grants payline somewhat, adding some to the anemic construction grants budget, possible new projects in chemoprevention, nutrition, and clinical research, and perhaps some modest expansion of intramural research all would compete for the extra money.

The committee report said that "the first priority of the Institute should continue to be the support of basic research, but with appropriate support for the application of research findings to reduce the morbidity and mortality from cancer."

The report (House Report No. 98-357) traces briefly the development of the National Cancer Program, describes recent research advances, and presents a positive picture of the program and NCI's role in it. Missing this year are the criticisms and sometimes noxious restrictions which the Labor & HHS Subcommittee have added in the past.

The report says the centers program provides "clones" of NCI throughout the nation, praises the clinical trials, training, cancer control, SEER, and research information dissemination programs, and singles out prevention, treatment advances, monoclonal antibodies, the virus program and subsequent discovery of oncogenes, and the discovery of a human leukemia virus as among recent accomplishments.

For all of NIH, the committee asked $4.3 billion, an increase of $386.3 million over the President's budget and $447.5 million over the FY 1983 total.

No date has been established for sending the bill to the House floor. The Senate Labor-HHS Appropriations Subcommittee has yet to mark up its bill, and may do that now that the House totals are firm.

DCCP'S BIOMETRY BRANCH, INCLUDING SEER PROGRAM, WILL MOVE TO DRCCA

NCI has concluded nearly two years of discussions (read that heated arguments, arm twisting, and back stage bloodletting) with Director Vincent DeVita's decision to transfer much of the Biometry Branch from the Div of Cancer Cause & Prevention to the Div. of Resources, Centers & Community Activities, including the prestigious, highly visible SEER Program.

SEER (Surveillance, Epidemiology, End Results) is a $10 million program which tracks cancer incidence and mortality around the U.S. It is a major component of DCCP's Field Studies & Statistics Program and is providing the all-important information on the impact of the National Cancer Program. SEER's incidence data are providing vital research leads for both NCI and extramural investigators. It has become one of NCI's premier efforts, and DCCP did not lose it and the top quality staff members who will transfer to DRCCA without a fight.

DCCP Director told his Board of Scientific Counselors last week that the transfer was being made "because the Cancer Control Program (housed in DRCCA) has been restructured to establish national goals for reductions in cancer incidence and mortality and help is needed not only to monitor these objectives but also to sharpen the focus on their intervention trials."

DeVita added that it was "a difficult decision to move one of our finest programs. It was not because we think lightly of it nor that it was not managed well. We feel it will best serve the Institute" by being located in the division responsible for applying research results, since SEER's goal is measuring changes in incidence and mortality.

Board member Louise Strong noted that the Board had recommended against the move. "We were concerned because we felt that the SEER people ought not be closely associated with the people who are applying research results." She said that SEER has been an "intrinsic part" of DCCP's epidemiology efforts, and suggested that the transfer was made because of "political pressures."

DeVita denied that political pressures had anything to do with the move. He said he had carefully considered the Board's position, and "as much as we need your advice and rely on it, we don't always accept it."

"We would much rather see you amalgamate biometry and epidemiology rather than separate it," Board member Carl Shy said. Separating etiology and prevention is difficult anyway."

Board member Pelayo Correa said he was concerned about the "impact on the possible loss of opportunity for research in etiology. I hope the opportunity for etiologists to monitor the data will continue."

"I guarantee that it will," DeVita said. Adamson said that "both divisions have agreed to preserve existing collaborations as well as to promote new areas within and across organizational components of NCI."

That concern has been a key factor in many interrelationships at NCI, and probably in most other federal bureaucracies—protection of turf, worship of the chain of command. Staff members of a branch in one division frequently are required (or feel that they are expected) to obtain permission from their own division superiors before they collaborate in any substantial way with or respond to requests from other divisions. DeVita, Adamson, and DRCCA Director Peter Greenwald offered assurances that epidemiologists in DCCP will be able to work directly with their colleagues in SEER without clearing it up and down the line.

Another factor in the change is the requirement that Biometry Branch staff members moving to DRCCA will have to move their offices to the Blair building in Silver Spring. The Blair building is considered the least desirable of the various locations occupied by NCI. To make room for them the remaining elements of the Div. of Cancer Treatment still located at Blair will move to the Landow building in downtown Bethesda, where SEER has been located.

During the long debate, DCCP argued so effectively that it would not be wise to split up Field Studies & Statistics that DeVita considered moving that entire program to DRCCA. "Our reaction," one DCCP staff member said, "was, 'Well, wait a minute. Maybe it wouldn't be so bad to split it up after all.'"

DCCP BOARD GIVES CONCEPT APPROVAL TO RFA FOR BIOCHEMICAL EPIDEMIOLOGY

The Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention last week gave concept approval to a new grant supported initiative in biochemical epidemiology with estimated first year awards totaling $1 million.

The Board also approved the concepts of new contract projects with estimated first year awards totaling nearly $2 million; approved recompetition of two contract programs totaling an estimated $700,000 in first year awards; approved doubling the money allocated previously to new AIDS contracts in the joint program with the National Institute of Allergy & Infectious Diseases, bringing NCI's contribution to $1 million a year; approved noncompetitive procurements worth about $700,000 a year; and deferred two new competitive contract projects for consideration at the Board's next meeting.

Biochemical Epidemiology, proposed first year funding, $1 million, three years. The Board approved issuing a request for applications. The staff narrative justifying the program:

Although a significant proportion of human cancers are thought to be attributable to life style and other environmental factors and are potentially preventable, the task of identifying the effects of specific factors and evaluating their relative importance is an enormous one. The process of induction and progression of human cancer is exceedingly complex; multiple exposure to a variety of agents over time is the rule rather than the exception, past exposure is dif- ficult to assess, host factors which may influence susceptibility are poorly understood, and the importance of promoting and/or anticarcinogenic exposures in humans have not been adequately defined.

Epidemiologic studies have resulted in the identification of factors which appear to increase or decrease cancer risk and have suggested the importance of host susceptibility factors. The usual epidemiologic techniques, however, have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states, in measuring low levels of risk, in evaluating directly host-environmental interactions, and in identifying dietary determinants of cancer. Fortunately, a variety of sensitive and specific laboratory methods are now becoming available which are likely to facilitate such epidemiologic investigations by providing better measures of exposure to initiators, promoters, anticarcinogens and inhibitors of carcinogenesis. Increased collaboration between laboratory scientists and epidemiologists in the application of these emerging techniques would be highly desirable.

Modifying factors related to diet and nutrition have been implicated in cancers of the stomach, large bowel, breast, endometrium and ovary. Hence, these types of cancer (among others) might be especially suitable for collaborative studies involving epidemiologists and experimentalists, including biochemists, analytical chemists, immunologists, and nutritionists.

Purpose of this RFA would be to stimulate development and/or use of objective measures of risk in epidemiologic studies of the etiology of human cancer.

Studies of interest include (1) pilot and feasibility studies which a) are necessary to adapt laboratory procedures to epidemiologic use, b) characterize the accuracy and validity of the tests, and/or c) compare the laboratory procedures with more traditional methods of assessing risk factors; and (2) fullscale epidemiologic studies using well characterized laboratory procedures. These procedures may measure actual levels of substances directly involved in the carcinogenic process, may measure markers, or factors which influence susceptibility. Collaboration between epidemiologists and laboratory scientists is encouraged at all stages in the development and use of tests in order to promote the efficient transition of research effort from laboratory to field study, although level of involvement of the epidemiologist will vary from consultation to project direction depending upon the stage of test development.

Board member Louise Strong asked, "If there is so much interest in this area, why should it not go through the R01 process?"

"This way, we'll get a special study section," said Genrose Copley, program director. "None of the standing study sections are prepared to handle this."

"We need a new study section then," Strong said. "Using an RFA is a bandaid over a bigger problem. We need a system to handle this on a regular basis, rather than a sporadic basis."

"That's a good point, and we're moving in that direction," Copley said.

"It's very hard to move study sections in this direction," DCCP Director Richard Admamson said.

Staff had asked only for $500,000 to fund first year awards. Board member Allan Conney suggested that, if there are a lot of good applications coming in, funding should be increased "four or five fold. Let's have a big bandaid."

Adamson said competition for research dollars from other NCI programs might preclude that kind of increase, but suggested doubling the request to $1 million. Board members agreed.

Copley suggested that DCCP might ask for an exemption from the reductions from study section recommended budget levels for this program. Hilary Koprowski, acting chairman in the absence of the new chairman, Barry Pierce, said, "That is a dangerous proposal. It could set a precedent. We're all getting letters requesting that exemption."

New competitive contract programs given concept approval were:

*Production of antibodies to oncogene products of retroviruses. First year award, $720,000, three years. The justification:

The oncogenes of retroviruses provide by far the greatest diversity of models for specific forms of tumorigenicity. A number of studies funded by the Biological Carcinogenesis Branch in the retrovirus area are involved with, or seek to explain, the molecular nature of the transformation process, possible explanations of how vi- ruses without definitive oncogenes can be in- volved in transformation, and the discovery of new oncogenes. Past studies on these viruses have shown that some of them possess genetic loci, or oncogenes, whose actions initiate and maintain the neoplastic phenotype of the infected cell. Other viruses are devoid of specific oncogenes, and in these cases the long terminal repeats or LTRs seem to be involved in oncogenesis. Both forms of viral oncogenesis are united by the persistence of at

least a portion of the viral genome in the host cell, either as an integral part of the host chromosome or as an independently replicating unit.

Oncogenes may be inserted into the replicative unit of retrovirus genomes in at least four distinctive ways. First, the onc may be inserted as an independently expressed gene that does not impose on either the structure or function of the replicative genes and is expressed from a subgenomic mRNA. The v-src of the Rous sarcoma virus is a well known example of this class. Second, it may be inserted as an independently expressed gene that replaces part or all of the replicative gene, and is expressed from a subgenomic mRNA. The v-myb of avian myeloblastosis virus is an example. Third, it may be inserted as a fusion between v-onc and a portion of gag that is accompanied by deletions in one or more of the replicative genes, usually pol and portions of gag and env, and is expressed as a polyprotein produced from genomic length mRNA. An example is v-myc from avian myelocytomatosis virus. Fourth, it may be inserted as two separately expressed v-onc domains, one fused with a portion of gag, the other expressed independently and the two together replacing portions of replicative genes. In this class, one gag-onc protein is produced from a genomic length mRNA. The second onc protein is produced from a subgenomic mRNA, for example erb-A and erb-B of avian erythroblastosis virus. With the exception of v-src, the insertion of oncogenes into retrovirus genomes creates genetic defects that preclude the production of virus unless the defective function is provided by a second helper virus.

Two immunological methods have been used to study the transforming proteins of oncogenic viruses: the development of hybridomas that produce monoclonal antibodies to the transforming proteins, and the production of antisera to peptides synthesized on the basis of the amino acid sequences of the transforming genes. Although some success has been obtained in developing both types of reagents, they are not generally available to the scientific community. The production and distribution of these reagents will permit dissection of the structure and function of transforming proteins at an otherwise inaccessible level of resolution. In addition, their application will standardize and help broaden the search for new oncogene products related to those already identified, and provide reproducible and economical reagents for the laboratories involved in these studies.

Purpose of this project will be to 1) produce the protein products (antigens) of selected oncogenes that may include, but not necessarily be limited to, src, erb-b, myb, fps, myc, erb-a, ros, rel, ras, ras^h, ras^k, abl, mos, sis, fos, and fes so that large quantities of the antigen will be available; and 2) prepare either monoclonal antibodies to the defined domains of these antigens or antisera to synthetic peptides. Each product will be characterized in detail and the products along with intermediate reagents such as transforming proteins, hybridomas, or synthetic peptides will be sent to a government repository for subsequent distribution.

These reagents will be made available to investigators under the payback system.

Project officers are John Cole and Garrett Keefer.

*Epidemiology survey of leukemia/lymphoma for HTLV. Proposed first year award, $200,000, three years. The justification:

A concept to study the epidemiology of the human T-cell leukemia/lymphoma virus was approved by the Board in May, 1982. Two contract awards have been made: the first to the Univ. of the West Indies, Kingston, Jamaica; the second to Gorgas Memorial Laboratory in Panama. Emphasis of the Jamaica project is on studies of virus associated malignancy and studies of the normal population to evaluate the distribution of the virus, and investigations of virus transmission particularly in the family and household setting. The first publication from this contract documents that 70% of unselected newly diagnosed non Hodgkins lymphoma cases have antibody to HTLV. Further manuscripts are being prepared to characterize the clinical and pathologic features of virus positive and negative cases. The Panama project will focus particular attention on the distribution of virus infection, the correlates of infection in the normal population, the potential role of intermediate host reservoirs of virus, and the possible role of insect vectors in virus transmission.

The current concept is being submitted as a supplement to the original concept in order to fund several disease oriented pilot surveys of virus infection. Our current data suggest that the sentinel disease associated with HTLV is a form of adult non Hodgkins lymphoma or lymphoid leukemia. The findings in Jamaica support the concept that HTLV antibodies are a useful marker for identifying clusters of this form of malignancy and presumptive HTLV endemic areas. Although seroepidemiologic studies using previously banked sera are underway to evaluate the occurrence of HTLV antibodies in various populations, these sera collections are, in general, relatively poorly characterized and provide only a rough indication of the possible occurrence of HTLV in these areas. A more directed approach would be to pilot targeted serologic surveys of adult lymphoid malignancies in areas which for either epidemiologic or initial serologic screening reasons or both are likely to have HTLV associated lymphomas. Two areas in particular, South America and China, provide this opportunity, with the resources in which this type of survey could realistically be undertaken. Preliminary serologic data from banked sera in Venezuela suggest the endemic occurrence of HTLV there. A survey of selected cases of lymphoid malignancy in Cali, Columbia, showed a cluster of positive cases in one geographically defined region characterized by heavy rainfall and an altitude of less than 2,000 feet. Several cases identified as antibody positive at NIH were from emigrants to the U.S. from several South American countries (Guyana, Brazil, Ecuador). All of this suggests that some areas in South America are likely to be endemic for HTLV. The geographic proximity of China to a major endemic focus of HTLV infection in Kyushu, Japan, offers the theoretical possibility that clusters of virus associated malignancy could occur in China. This is supported by the curious clustering of high rates of leukemia and lymphoma in the eastern provinces of Jiangsu and Anhui which share the same latitude as Kyushu. Furthermore, preliminary data from the retrospective review of 553 lymphoma cases from five geographic areas of China demonstrate possible regional variation in the prevalence of cases with T-cell morphology. The highest rates were

reported in Shen Yang, Quingdau, Suzhou, and Kuming. Thus preliminary epidemiologic data suggest the possibility of cluster areas for HTLV associated leukemia and lymphoma cases in China.

The survey design proposed to be undertaken in South America and China will pinpoint suitable hospitals to cover a broad population in all ecologic zones. The disease to be tested will be all new and prevalent cases of non-Hodgkins lymphoma, chronic lymphocytic leukemia, lymphoma cutis, cutaneous T-cell lymphoma, and any other lymphoproliferative malignancies occuring in adults. For this survey, cases will be restricted to persons over the age of 18. Systematic data will be collected or abstracted from the records on each case including basic demographic and diagnostic information, residency history, medical diagnosis, and clinical and pathologic features. For each case, serum will be collected on an age and sex matched normal control from the region. In addition, we plan to test serum samples from a blood relative of a case in approximately one quarter of the cases. Sera samples from China will be prescreened there with positive samples forwarded to NCI for confirmation. Samples from South America will be sent directly to NCI for testing.

It is anticipated that the results of this survey will identify areas for future more in depth studies and provide some estimate of the regional variation in HTLV occurrence and the ecologic, geographic and racial correlates. Using this survey approach, contract resources can be efficiently marshalled to areas where the greatest scientific productivity can be achieved. In this regard, if a particular hot spot for the disease or virus should come to our attention through the laboratories that we work with, we could scale back the efforts in China or South America sufficiently to allow us to evaluate these special situations.

Project officers are William Blattner and Jeffrey Clark.

CONCEPT REVIEW FIGURES ARE ESTIMATES

The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the project in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when they are cleared for publication.

* Epidemiology of human T-cell leukemia/lymphoma virus. Proposed first year award, $400,000, three years. The justification:

This project involves close collaboration with Robert Gallo, chief of the Laboratory of Tumor Cell Biology in the Div. of Cancer Treatment, who discovered HTLV. All molecular biologic and virologic studies, including testing of all tissue and serum samples for HTLV, are to be performed in Gallo's lab. Epidemiologic studies are to be designed and executed, in collaboration with Gallo, by the staff of the Environmental Epidemiology Branch. This project involves multiple contracts which are to be competitive, and will be awarded to organizations having departments of pathology, epidemiology and/or infectious disease in HTLV endemic areas in the U.S. and abroad, regional health agencies to serve as liaison to selected health organizations or universities in virus endemic areas, or government medical science agencies with nationwide health authority.

This concept deals with allocations of funding for a series of epidemiologic, clinical and experimental studies aimed at defining (1) the distribution and determinants of HTLV infection, and (2) the role of HTLV as a cause of cancer.

High risk areas are identified by the occurrence of a characteristic type of T-cell malignancy and the presence of HTLV antibodies in the normal population and in cases. Targeted interdisciplinary epidemiologic studies are to be undertaken in these high risk areas through a series of contracts with qualified collaborators. In general, contractors will be selected because (1) they have access to defined populations of patients with malignancy, and corresponding clinically normal populations, and (2) they have the capacity or potential for precisely defining the nature of the malignancy, particularly with regards to T and B lymphocyte typing. Other types of investigations to be funded include follow back studies of virus positive individuals detected in prospectively collected samples, and studies of populations migrating into or out of virus endemic areas.

Since virus endemic areas are frequently located in countries where medical research facilities may be rudimentary at best, a portion of the funds allocated to this project will be used for purchase of equipment for specimen processing and storage, and for immunopathologic typing. Other expenses will include hiring of personnel to assist in specimen and data collection, and for travel and shipping costs. In general, samples for HTLV testing will be sent to Gallo's lab, while T and B typing will be performed in the collaborator's lab.

This project is targeted at developing a parallel series of sero-epidemiologic and interdisciplinary studies in selected regions of the world. By coordinating studies of this candidate human tumor virus, it should be possible to delineate the patterns of virus prevalance and T-cell leukemia/lymphoma, and to clarify etiologic relationships.

Blattner is the project officer.

* O-dianisidine and O-tolidine dye worker exposure study. Proposed award $60,000, one year. This and the following six projects will be funded with NCI funds through the agreement with the National Institute of Occupational Safety & Health. Justification:

Many synthetic organic dyes used in the U.S. contain benzidine, a regulated human carcinogen, or analogues of benzidine such as O-tolidine and O-dianisidine. It is clear that benzidine causes bladder cancer in humans while O-tolidine and O-dianisidine, which have similar chemical structures, also exhibit carcinogenic properties in animals. In addition, these same analogues are positive on microsomal mutagenicity assays. Therefore, they should be regarded as presenting a carcinogenic risk to humans. The benzidine analogues are used extensively in the manufacture of dyes. This is

accomplished by attaching chemical substitutes by diazo linkage to the benzidine analogue. The dye molecule may not possess toxic properties, however, it can be metabolically reduced in vivo back to the parent analogue. Several studies have demonstrated a severing of the diazo linkage in the dyes by intestinal microflora and to some extent by hepatic microsomal enzymes. Based on studies of several different animal species, it is believed that humans exposed to O-tolidine and/or O-dianisidine based dyes metabolize the dye to free O-tolidine and/or O-dianisidine. These carcinogens are then excreted in the urine.

The objectives of this study are (1) to characterize levels of exposure of workers to dyes made from the two benzidine analogues; (2) test the urine of these workers for their metabolites and attempt to correlate urine levels with environmental levels or other exposure factors; (3) test the urine of workers for mutagenicity based upon the Ames test. Variability in the composition between the batches or lots of dyes is commonly found. To account for the variability, bulk samples of the dyes will be analyzed for the dye compound, free benzidine analogues, and inert materials. The method that NIOSH will use to analyze for benzidine analogues is capable of detecting dye metabolites in urine at concentrations as low as five parts per billion. In addition, there is a method for detecting benzidine analogues at the 100 parts per trillion level.

Factors that may affect mutagenicity of the workers' urine such as diet, smoking habits, and the use of medications, will be recorded on the participant questionnaire. We propose to identify 50 exposed and 50 nonexposed workers for the study. Any excess urine not used for mutagenicity testing will be frozen and stored for future analyses if necessary.

Elizabeth Weisburger is the NCI project officer.

* Mortality and IH evaluation of workers exposed to lead chromate paints. Proposed first year award, $100,000, three years.

To evaluate the long term health effects, in particular mortality from lung and other respiratory cancers, of exposure to paints containing lead chromate pigments, NIOSH is proposing to conduct retrospective cohort mortality and industrial hygiene studies at three Midwest farm implement manufacturing facilities. The mortality study will include a cohort of about 2,200 painters employed at the three plants from 1940 to 1982. Historical exposures of painters to lead chromate will be estimated based on industrial hygiene records, engineering drawings, histories of paint usage, and the collective memories of long term employees as outlined in the protocol. To the extent feasible, the information will be used to analyze health outcomes in subgroups within the overall cohort, and develop dose response information.

If this study indicates that lung cancer is in excess and the excess is in the range of risks that could be explainable by smoking, then the effects of smoking will be assessed. The assessment will be accomplished via an interview survey of a random sample of the cohort. In this survey we will interview those study subjects who are still alive and interview the next of kin of study subjects who are deceased. If the smoking habits of the study population are found to be different from the U.S. population, adjustment of the mortality ratios will be performed according to a method described by Axelson. In addition, if a positive dose (occupational exposure) response (lung cancer mortality) is observed, smoking becomes a less important confounder in this study.

Robert Spiritas is the NCI project officer.

* Case control study of lung cancer and diesel fumes. Proposed first year award, $50,000, two years.

Several previous mortality studies show that truck drivers suffer an excess of lung cancer. There are two suspected agents, cigarette smoke and diesel fumes. We propose to do a case control study which controls for smoking and which determines whether diesel fume exposure is associated with lung cancer mortality. Past lung cancer case control studies have not specifically focused on diesel exposure but instead have identified truck driver or vehicle driver as occupational categories with excess risk without reference to diesel motors. This proposed study will specifically identify drivers of gasoline vs. diesel trucks. The cases will be 500 lung cancer deaths among Teamsters over the last five years. These cases will be matched to controls who died of other causes. Interviews of next of kin will be conducted to determine smoking habits and an attempt will be made to determine the working conditions of each participant, especially in regard to the stage of the truck (e.g., air conditioned cab, new truck, etc.).

Extracts from diesel fumes cause cancer in animals, and diesel fumes are higher in polynuclear aromatacs, which are known human carcinogens, than are fumes from gasoline engines. The Teamsters Union, which has excellent work histories and is supportive of this study, includes truck drivers with moderate diesel exposure, garage mechanics with high diesel exposure, and a number of warehouse and other workers with low or no diesel exposure. Industrial hygiene surveys will be conducted to estimate the exposure levels to diesel fumes and other contaminants among various Teamster occupational groups. Specifically, 17 individual PNAs, NO2, CO, total hydrocarbons, and nitropyrene will be measured.

Debbie Silverman is the NCI project officer.

* Ethylene oxide mortality study. Proposed first year award, $70,000, three years.

Ethylene oxide is used as a sterilant industrially. We propose to study the mortality experience of individuals who have been exposed while sterilizing. From two animal and two human studies, it appears that ethylene oxide is a leukemogen. Excess mortality in one human study was found for leukemia, stomach cancer, all cancers, and cardiovascular disease. However, all human studies done so far are flawed by small sample size and mixed exposures, problems which we hope to overcome in our study.

We have conducted an assessment to determine the feasibility of doing a retrospective cohort mortality study of workers exposed to ethylene oxide. In the course of this assessment, we have identified a number of plants (study populations) that satisfy the criteria for inclusion into the cohort.

The plants in the cohort use or used EtO in industrial sterilization. Most of the plants sterilize medical products, although a few use EtO to test and repair sterilizers or to sterilize spices. We believe this cohort is the best available cohort for a mortality study of EtO exposed workers. It is the largest such cohort in the smallest number of plants, and it

includes workers exposed primarily to EtO alone.

In the course of a nine month feasibility study we have visited 11 plants and received information on the number of workers exposed to EtO from approximately 75 companies. We propose to study individuals who worked prior to January 1978 at 34 plants. These plants are the larger ones with a longer history of EtO use. The individuals who worked at these plants, primarily men, have been divided into a more highly exposed group (usually sterilizer operators) and a second group of low or intermittent exposure (usually material handlers, maintenance, quality assurance personnel, etc.). The more highly exposed group has accumulated approximately 9,000 person years since first exposure, whereas the less exposed groups have accumulated approximately 87,000 person years. Using 1970 U.S. leukemia mortality rates for males aged 45-49 (5.6 per 100,000), we expect about .51 deaths in the high exposure group and 4.90 in the low exposure group. Using an alpha of .05 and a power of .80, we will be able to detect a relative risk of 2.35 for the total cohort and of 7.50 for the high exposure group.

This is a young cohort with relatively short latency, although the disease of primary concern is leukemia, which is assumed to have a much shorter latency than other cancers. In addition to ascertaining the current vital status of this cohort, we plan to ascertain vital status in the future at five year intervals. Future followup will include not only the individuals listed above who were first exposed prior to 1978 (minimum six years latency), but all other individuals exposed at these plants from 1978-1983. These records will be collected at the same time we collect the records of the cohort discussed above. Future analyses, at five year intervals, will include more person years and will have more statisatical power to detect a lower relative risk than the initial cohort.

If the results of this study indicate that diseases associated with smoking are in excess, and the excess risks are in the range to be explainable by smoking, then the effects of smoking will be assessed. This assessment will be carried out using the same methodology described in the lead chromate paints study.

Aaron Blair is the NCI project officer.

Board member Lee Wattenberg asked who might submit proposals for the study, after the NIOSH project officer, William Halperin, had said it would be "the most extensive industry watch ever done." Halperin said that support service companies, "Westat, for example," probably would be interested in submitting proposals.

The remainder of the DCCP concept presentations will be published next week in The Cancer Letter.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CP-41002-72

TITLE: Induction, biological markers and therapy of tumors in primates
DEADLINE: Nov. 21

NCI has a requirement to solicit proposals to provide a broad data base on the carcinogenic risk to humans of a variety of chemicals and drugs. The results obtained from this project will serve to identify agents with high carcinogenic potential, and will provide the basis for removal of such agents from the environment or from clinical use, thereby reducing the incidence of cancer in humans.

Specific objectives are 1) to obtain comparative data on the response of nonhuman primates to known carcinogens and to materials suspected to be carcinogenic in humans, 2) to evaluate the chronic adverse effects of antineoplastic agents which are being used clinically for long-term remission, in adjuvant therapy, and in the treatment of non-malignant conditions such as chronic glomerulonephritis, psoriasis, and diffuse collagen disorders, 3) to obtain model tumor systems in nonhuman primates in order to ascertain the potential usefulness of various treatment modalities in man, 4) to develop models for chemoprevention therapy, 5) to develop biological markers and diagnostic tests for detecting preneoplastic changes as well as frank neoplasia and for monitoring nonhuman primates and cancer patients prior to, during and following therapy; and 6) to study the metabolism of known or suspected carcinogens in nonhuman primates and to characterize the interaction of test compounds with macromolecules in vivo.

It is expected that one award will be made for a three year period. Contractor's facilities must be within close proximity of the NIH campus, Bethesda, Md., so that daily consultation and visits may be made by the government project officer.

CONTRACT SPECIALIST: Jackie Ballard
RCB, Blair Bldg. Rm. 115
301-427-8888

NCI CONTRACT AWARDS

TITLE: Primary Genetic Centers
CONTRACTOR: Charles River Breeding Laboratories, Wilmington, Mass., $7,365,143.

The Cancer Letter _Editor Jerry D. Boyd

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