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NCI IMPLEMENTING CHANGES IN ORGAN SITE PROGRAM, DIRECTING GRANT APPLICATIONS TO NIH STUDY SECTIONS

NCI has started implementing the major changes in the Organ Site Program recommended by the National Cancer Advisory Board, taking a chance that Congress will not direct through impending legislation that the program continue in place as it is.

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In Brief

ACR MOVING TO D.C.; FDA ADVISORS OK VP-16 NDA; WIERNIK TELLS MISSOURI NO; DEWYS MOVES TO DRCCA

AMERICAN COLLEGE of Radiology will move its headquarters from Chicago to Washington D.C., probably within two to four years. The ACR Council recently approved the move and directed College executives to start searching for a site in D.C. or suburbs. . . . **FDA ONCOLOGIC DRUGS** Advisory Committee unanimously approved Bristol Laboratories' new drug application for VP-16. The approved indications are for treatment of refractory testicular tumors and for small cell lung cancer in combination with other drugs. FDA, which pushed the NDA process through at a record pace probably will accept the committee's recommendation and approve the drug within a month. The committee also approved Lilly's NDA for vindisine sulfate for ALL no longer responsive to oncovin; approved Lederle's NDA for high dose methotrexate for non-Hodgkin's lymphoma in combination therapy (although the committee's request for further information probably will delay FDA concurrence); and rejected Mead Johnson's NDA for ifosfamide for treatment of non-small cell lung cancer. . . . **PETER WIERNIK** has removed himself from consideration for director of the Missouri State Cancer Center, probably clearing the way for appointment of Ronald Vincent, chief of thoracic surgery at Roswell Park Memorial Institue, to the position. State Rep. Joe Holt, chairman of the Missouri Cancer Commission, was quoted in a Columbia, Mo. newspaper that Wiernik had withdrawn because the commission could not meet his demands. Holt had previously told the press that Wiernik and Vincent were the candidates and that Wiernik, former director of the Baltimore Cancer Research Center, had laid down three conditions for taking the job (***The Cancer Letter***, Sept. 10). . . . **WILLIAM DEWYS**, who has been chief of the Clinical Investigations Branch in NCI's Div. of Cancer Treatment, has moved over to the Div. of Resources, Centers & Community Activities as associate director for cancer prevention and head of the Preventive Medicine Program. DeWys' responsibilities will include heading chemoprevention activities, including clinical trials. . . . **EDWARD SONDIK** will transfer from the National Heart, Lung & Blood Institute to become chief of DRCCA's Biometrics & Operations Branch.

Obey Questions NCI Honesty, Transfers IARC Monograph Support To NIH

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ORGAN SITE GRANTS GOING TO NIH, NCI PLANS RFA FOR COORDINATING CENTER

(Continued from page 1)

Director Vincent DeVita told the NCAB last week that grant applications submitted under any of the four projects—National Bladder Cancer Project, National Prostatic Cancer Project, National Large Bowel Cancer Project, National Pancreatic Cancer Project—are now being directed to the appropriate NIH study section for review, rather than one of the four nongovernment headquarters.

Steps are under way to phase out the four headquarters and to develop a national competition for a new headquarters for the "Organ Systems Program."

Meanwhile, with Congress in recess, no action will be taken on renewal of the National Cancer Act until the legislators return in a post-election session, starting Nov. 29. When the renewal bill reaches the floor of the Seante, at least one amendment will be offered which would write into law continuation of the four national projects, and perhaps add a fifth for breast cancer.

Discussions between staff members of Sen. Daniel Moynihan (D.-N.Y.) and Edward Kennedy (D.-Mass.) apparently have produced a compromise amendment which would preserve the four projects, and may add another for breast cancer if lobbyists for that proposal are successful, but would require grants to be reviewed at NIH. The amendment would include a line item authorization of $20 million a year for the present projects, probably more if breast cancer is added.

After a study initiated by the NCAB a year ago, in which a group of outside consultants reviewed the four projects and made recommendations for improving the program, the Board recommended that the program be renamed the Organ Systems Program, the four headquarters consolidated into one, review be returned to NIH, and the program be made more flexible to permit new organ systems to be added and old ones dropped, as needs change.

Key features of NCI's plan to implement the recommendations:

- Establish an Organ Systems Coordinating Center through a cooperative agreement at an institution outside the government. A request for applications will be published, requiring applicants to submit letters of intent, probably due by Jan. 1, with an application deadline of March 1. Peer review would make the selection, which would go to the NCAB in October 1983. The Coordinating Center would be administered by a director.
- The Breast Cancer Task Force, which unlike the four organ site projects has been administered entirely within NCI, with outside advisory groups, would be integrated into the new Organ Systems Program.
- An Organ Systems Coordinating Group would be established by the OSCC director. The group would be composed of scientists from around the country. The coordinating group would form three working groups initially, gastrointestinal, genitourinary, and breast. Each of the working groups would utilize members from the existing task forces as well as new members and would be assisted by an NCI executive secretary. The chairman of each working group would be a member of the Organ Systems Coordinating Group which would provide overall planning and coordination for the program and provide continuous evaluation to identify organ systems deemed to be in need of special emphasis as well as areas no longer requiring special attention.

- The individual working groups would have responsibility for program planning and coordination, planning and conducting workshops and conferences, publications, identification of areas deemed appropriate for technology transfer, and annual reporting to NCI. They will develop multidisciplinary program plans focusing research on the cause, prevention, detection, diagnosis, and treatment of cancer in the various organ systems.
- Those plans would be presented to the appropriate NCI Boards of Scientific Counselors for concept approval. Once approved, RFAs and program announcements would be published to encourage grant applications as determined.
- Grant applications submitted in response to those announcements would be reviewed for scientific merit as R01 applications by study sections within the NIH Div. of Research Grants, or as P01 applications by review committees within the NCI Div. of Extramural Activities.
- The two cooperative groups conducting clinical studies in the Organ Site Program, in bladder and prostatic cancer, will be transferred to the Div. of Cancer Treatment and will be supported through cooperative agreements, as are the other cooperative groups.

- During the transition, the four existing headquarters would be maintained until the new OSCC becomes operational. During that time, the headquarters would continue their planning activities including conducting workshops and conferences. Current project working cadres would remain active.

Kash Mostofi, ex officio member of the NCAB from the Armed Forces Institute of Pathology, said, "I'm scared stiff about applications in the Organ Sites Program going to the pathology study section at NIH. Approval would be way down." Organ site grants "are studying things we need to know, but they do not meet the requirements of the study section."

Some leaders of the four projects have argued in favor of assigning review of all organ systems grants to NCI Div. of Extramural Activities committees. DEA Director Barbara Bynum said that she feels NCI

can work with DRG in properly assigning applications to study sections.

The Organ Systems Program will be a responsibility of the Div. of Resources, Centers & Community Activities, in the Organ Systems Branch. The DRCCA Board of Scientific Counselors last week unanimously approved the new plan after a vehement denunciation by Charles Moertel of the attempt to overturn the NCAB decision through congressional intervention.

"This whole business was decided in a political arena," Moertel said. "Great political forces exerted themselves. I can see where we may have continued political dominance." The Moynihan amendment would, "in essense defeat and overturn one of the most positive steps the Institute has taken. It is appalling, that we get ourselves in a situation where science can be manipulated by politics."

OBEY MOVES SUPPORT OF IARC FROM NCI TO NIH OVER BENZENE CONTROVERSY

Congressman David Obey (D.-Wisc.), following up on his charge that NCI officials had interfered with publication of a monograph on benzene by the International Agency for Research on Cancer (***The Cancer Letter,*** Aug. 20), persuaded the House Appropriations Committee to direct that NCI's $400,000 a year cooperative agreement with IARC funding the monograph series be administered by NIH.

Obey also inserted language in the committee's report on the bill which asks IARC to "develop written protocols for the precise procedures to be followed by the Secretariat in the selection of topics to be considered by working groups, the selection of participation on working groups and the proceedings for revision of any documents approved by a working group."

NCI Director Vincent DeVita told the National Cancer Advisory Board last week that "We're very sorry to see that language in congressional action. It represents an attempt to interfere in monograph writing by IARC. There is no basis for action. We are only one twelfth of IARC, and other countries feel the United States should not attempt to dictate to them."

DeVita insisted "There is no evidence of any tampering by NCI, and we did not interfere with the process."

Obey based his charges on an internal memo by a chemical company executive which said that Richard Adamson, director of NCI's Div. of Cancer Cause & Prevention, had instructed his representatives to an IARC meeting on the benzene monograph to express the Institute's opposition to risk estimates.

After that meeting, an annex was added to the monograph which deleted an estimate that lifetime exposure to benzene at levels as low as 10 ppm could result in 17 additional cases of leukemia. The annex did include the estimate of 140 to 170 additional leukemia cases at an exposure of 100 ppm. The main body of the report included both estimates.

Obey charged that IARC officials were intimidated by NCI's alleged position and, fearing loss of U.S. support, made the change without consulting the scientists who wrote the report.

"It is important that people exposed to chemicals such as benzene be assured that the evaluation of research done on those chemicals is performed in an honest and proper scientific manner," Obey said. Taking administration of the support of IARC away from NCI and giving it to NIH would do that, he indicated.

"What we found in the benzene investigation," Obey said, "was a group of scientists who were experts charged with making a decision voting to say that people exposed to benzene at the current level allowed in factories will suffer a much higher incidence of leukemia than people who are not. There was no attempt to challenge that finding through the proper channels or in the light of day. The arguments were not presented to the scientific panel; they were made through the back door to the administration staff of the agency."

Obey said the internal memo from the chemical companies which discussed the efforts to be made by certain National Cancer Institute employees pointed out that these employees controlled the U.S. contribution to the program. "There is in my mind little question that the possibility of withholding the U.S. contribution played a role in this very disturbing matter," Obey said.

Thus, Obey, a severe critic of the chemical industry is in the position of basing his charges on a memo purportedly written by an employee of a chemical company.

Adamson has adamantly denied the charge. In a statement he made to the DCCP Board of Scientific Counselors last month, Adamson said:

"In October 1981 benzene was among a series of industrial dyestuffs and chemicals evaluated by IARC. Also at this meeting, as an experiment, for the first time they did a quantitative risk assessment on benzidine and benzene. NCI had an observer at that meeting but did not interfere with the risk assessment. This monograph was published on schedule in July 1982; therefore, publication was not delayed as our critics have charged. In addition, in the annex to the monograph, there was a significant change in one sentence in which a linear extrapolation to 10 parts per million for risk of excess deaths, present in the initial draft, was deleted; the published version extrapolates to 100 parts per million. NCI did not suggest this change; in fact, we did not know of the change until we received the final copy of the monograph.

"In January 1982 a group of representatives from

industry met with me to voice scientific concerns over one of the papers used in IARC's risk assessment. We discussed, briefly, potential animal models for benzene leukemogenicity, the fact that this was the first time that IARC had done a risk assessment, difficulties with quantitative risk assessment and they voiced several scientific concerns with the Rinsky paper. I declined to get involved with their concerns. The meeting did not last long since that same day I had to attend a risk assessment meeting called by the Deputy Assistant Secretary for Health, Disease Prevention and Health Promotion (Dr. Michael McGinnis) to look at risk assessment activities throughout the Dept. of Health & Human Services.

"At his request, Dr. Lorenzo Tomatis, director of IARC, who was visiting in this country, came to see me on March 8, 1982, for about 15 minutes. Since he was a new director and I was a new director of this division, he wanted to meet me and to express his concern about the switch in funding mechanism to the cooperative agreement since the contract was due to expire. We extended the contract for one month, to July, since there was an IARC meeting at the end of June. I explained the mechanism of the cooperative agreement to him and the fact that it would now be reviewed like a grant by an outside committee and would come to the May 1982 National Cancer Advisory Board meeting for final peer review. We also briefly discussed quantitative risk assessment and we both agreed that IARC should have a separate meeting and a complete monograph on this area. This also was advice the working group gave to Dr. Tomatis. I subsequently followed up on this conversation with a letter to Dr. Tomatis in April 1982, which I have sent to all the Board members.

"In summary, the NCI did not attempt to delay any publication by IARC nor is the NCI responsible for any change in the annex to the monograph. We do not have nor do we seek to have editorial control over IARC. We do continue to be concerned with the process of quantitative risk assessment and did convey this concern to IARC as an issue unrelated to the specifics of the risk of exposure to benzene. Recent reports in the popular press and in *Science* magazine are inaccurate."

"I can't be responsible for what someone writes in a memo," Adamson told ***The Cancer Letter.*** "What they said I said is totally untrue."

DCCP BOARD GIVES CONCEPT APPROVAL TO $5.5 MILLION IN CONTRACTS, GRANTS

The Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention gave concept approval to new and continuing projects totaling more than $5.5 million in first year funding, including a new grant supported project in the Carcinogenesis Extramural Program.

The Board approved issuing a request for applications to solicit proposals for studies of the hepatitis B virus and primary hepatocellular carcinoma, specifically biological investigations of virus host interactions and mechanisms of causation of human cancer. DCCP would earmark $500,000 to support the first year of grants which may be awarded under the RFA. The staff's description of the project:

Currently, epidemiological investigations link hepatitis B virus infections with primary hepatocellular carcinoma in man. This linkage was discussed at an NCI conference May 3-4, 1982. The consensus was that hepatitis B virus was the best model in humans of a specific agent related to a specific cancer. In addition it was felt that there was a lack of understanding of the biological mechanisms for the disease processes attributed to hepatitis B virus and that all of these mechanisms are worthy of further investigation. The intent of this RFA would be to encourage research to determine: (a) whether or not hepatitis B virus is a complete carcinogen in humans; (b) the molecular mechanisms underlying the interaction of the virus with hepatocytes in human and animal model systems; (c) the characteristics of model systems already developed in terms of their suitability for studying the development of hepatocellular carcinoma and establishing their relevance, if any, to human disease; (d) the gene products of the hepatitis B virus in terms of their function and whether any of the gene products are transforming proteins.

The following representative research is projected: (1) studies to determine whether the hepatitis B virus is a complete carcinogen in cultured human liver cells or in animal model systems; (2) investigations on the mechanims(s) of oncogenesis by HBV including the role of integrated DNA in transformation, examination of virus coded proteins for transforming potential and development of in vitro model systems for transformation; (3) studies on the progression of acute hepatitis through chronic hepatitis to primary hepatocellular carcinoma, including studies on why tumors develop in only a limited number of individuals infected with the hepatitis B virus (possible host determinants of the process) and on the mechanism(s) by which chronic infections are maintained in the immunologically competent host; (4) studies on the cytopathology of the disease to shed light on the mechanism of liver damage, e.g., to determine whether virus replication, natural killer cells, cytotoxic T cells or other mechanisms might be involved.

These studies should provide the biological equivalent of the very strong epidemiologic evidence which now links hepatitis B virus to primary hepatocellular carcinoma in man and should also provide objective criteria for the evaluation of present and future vaccines which may be useful in the prevention of this disease.

John Cole is the program director.

The Board deferred an RFA for an epidemiologic study of childhood cancer, calling instead for a workshop to discuss the issue and make recommendations.

The Board approved nine new contract supported projects with a first year estimated total cost of $1.5 million.

Support services for clinical epidemiologic studies. Estimated first year award, $211,000, three years.

The Clinical Epidemiology Branch (1) conducts independent and cooperative research into host factors (personal, familial, or ethnic) in the development of cancer, as revealed by peculiarities in cancer occurrence, especially with respect to preexisting disease, and by laboratory tests designed to elucidate subclinical abnormalities that portend high risk or reveal new understanding of the pathobiology of cancer; (2) seeks

epidemiologic evidence for the interaction of host factors with environmental agents; (3) through epidemiologic techniques, tests hypotheses generated in experimental laboratories for their applicability to man, and provides concepts from human observations for elucidation in the laboratory; and (4) stimulates clinical epidemiologic research nationally. Initiating support services by contract is necessary now for three reasons: (1) Research in the genetics of human cancer is increasing as new laboratory techniques emerge. (2) The program is expanding to include studies of reproduction in cancer patients and of hepatitis and hepatoma in veterans. (3) Our site visitors noted that our researchers lacked sufficient support services to follow through with long term investigations of intriguing leads from bedside observations on cancer etiology.

The proposed contract will provide a broad range of services: (1) preparation of data collection forms, such as questionnaires and abstracting forms, with accompanying manuals; (2) assistance to accomplish interviewing, medical record abstracting, data and technical editing, and collection and transport of biologic specimens; and (3) aid in data management, e.g., systems design, programming, data entry, proofing, editing, updating, records management, tabulations, and statistical presentations. Progress reports will be prepared as specified by the project officers.

Project officers are John Mulvihil and Dilys Parry.

Effects of plant flavonoids and derivatives on endogenous nitrosation. Estimated first year, $50,000, two years.

Endogenous nitrosation of secondary or tertiary amines by nitrite, either administered as such, or formed by bacterial reduction of nitrate contained in vegetables or cured meats, has been well documented. On the other hand, under the proper conditions vitamin C and polyhydroxy compounds such as propyl gallate inhibit the endogenous formation of nitroso compounds by competing with the amine for the nitrite. There are also some reports indicating that vitamin C may enhance nitrosation.

Epidemiological studies indicate that certain human populations who are generally vegetarian tend to have a lower incidence of cancer than the general population. Vegetables, fruits and other plant products generally contain small amounts of numerous plant flavonoids which are also polyhydroxylated compounds. The possibility that these flavonoids or their derivatives may hinder endogenous nitrosation and thus decrease exposure to probable carcinogens has not been investigated. It is proposed to test typical plant flavonoids (kaempferol, quercetin, luteolin, hesperitin, for example), in a model animal system to determine whether endogenous nitrosation might be inhibited or enhanced.

Elizabeth Weisburger is the project officer.

Characterization of business establishments with linkage to the National Occupational Exposure Survey. Estimated first year, $176,000, one year.

It is our intent to issue an RFP requesting a complete characterization of business establishments in the United States at the four digit level for the period October 1982 through September 1983. These data must provide continuity with previously maintained files in this regard.

NIOSH has maintained a full file which belongs to Dun & Bradstreet, which has provided this characterization of business establishments from 1978 through September 1982. This file consists of approximately 4.3 million records and accommodates up to six SIC codes in the characterization of each business establishment.

NIOSH is currently completing the field phase of the National Occupational Exposure Survey (NOES). The additional data requested by the RFP in conjunction with the previously acquired data will provide a base which population estimates of numbers of persons potentially exposed to compounds of interest may be generated from the information collected from the NOES. This resource will be utilized by noth NIOSH and NCI in the design and implementation of epidemiologic studies with occupational emphases by facilitating the selection of corhorts with exposure(s) to substances of interest.

Thomas Mason of NCI and David Sundin of NIOSH are the project officers.

Characterization and validation of carcinogen-induced transformation of human cells in vitro. Estimated first year, $137,708, two years, competitive.

The purpose of these experiments is to characterize and validate a human cell transformation system that detects carcinogens and to determine both the culture and cellular factors that influence the quantitation of this system. Validation of the in vitro human fibroblast assay for carcinogen-induced anchorage-independent growth will require that the anchorage-independent phenotype by systematically evaluated to determine the basis of the phenotype and the sensitivity and specificity of the anchorage-independent endpoints in assessment of carcinogen-induced damage. Validation of this assay will include determination of (a) the fidelity of the assay to detect direct acting carcinogens from diverse chemical classes and (b) the specificity of the assay by testing carcinogens, noncarcinogenic agents, and promoters. The potential of anchorage-independent cells to further progress towards malignancy will be assessed using carcinogen-altered anchorage-independent fibroblasts. The necessary stages in this assessment include: (a) improving the sensitivity of the nude mouse assay for human cell tumorigenicity, (b) evaluating the stability of the anchorage-independent phenotype and the potential for anchorage-independent cells to spontaneously progress to the malignant state, and (c) determining the effect of secondary changes induced by carcinogens or tumor promoters on the progressive development of the malignant phenotype.

An assay to directly assess human risk from exposure to potentially mutagenic and/or carcinogenic agents is currently not available. As an alternative, a model system to quantitatively measure mutation and neoplastic transformation of human cells in culture following carcinogen or mutagen exposure would be useful. The previous reports have identified two basic phenotypes: morphological transformation and anchorage independence. Morphological transformation of human cells occurs at a low frequency, is not always reproducible, and requires a long latency period before scoring. However, morphologically transformed cells frequently give rise to progressively growing tumors in nude mice.

Several quantitative studies have used the anchorage-independent phenotype to monitor carcinogen induced cell transformation. These studies have shown a correlation between carcinogen dose and the frequencies of both induced mutation and anchorage-independent growth. Considerable evidence currently indicates that various carcinogens induce anchorage-independent growth, however, validation of anchorage independence as a specific carcinogen-induced phenotype is lacking. Also a definite correlation between anchorage-independent growth and tumorigenicity is not available for human cells. The observations of Peehl and Stanbridge and our unpublished results have indicated that normal foreskin fibroblasts can grow in semi-solid medium if the growth conditions are optimized. The results of Stanbridge and Wilkinson using human cell hybrids have also indicated that anchorage independence and tumorigenicity are independent phenotypes, and although necessary, anchorage independence may not be a sufficient determinant for tumorigenicity.

It has been shown that anchorage-independent cells can give rise to progressively growing tumors, but it is not known whether they are tumorigenic at the time they acquire the anchorage-independent phenotype or if the tumorigenicity is a secondary change, as suggested by Stanbridge and Wilkinson.

The low frequency of progressively growing tumors in nude mice following injections of up to 10^7 carcinogen-altered anchorage-independent cells suggests that either the cells are "preneoplastic" and requre additional exposure to carcinogen or need additional time to express the neoplastic cells. Many of the cells from human tumors also fail to produce any tumors in nude mice. The mechanism for the generation of these false negatives is felt to be due to the residual immune system and the presence of natural killer cells. Many previous evaluations of the tumorigenicity of human cells have involved subcutaneous inoculation into nonirradiated or irradiated nude mice. Attempts to increase the sensitivity of the nude mouse model have included inoculating cells into the anterior chamber of the eye and observing tumors directly, or inoculating cells into the brain and observing the mice for neurological dysfunction.

Although recent advances have been made in the development of quantitative assays for studying the transformation of human cells in culture, several important parameters remain to be defined: (a) the stability of the transformed phenotype; (b) the mechanism for its induction, i.e., epigenetic or genetic; (c) the effect of aging on cellular transformation; (d) the correlation of tumorigenicity and anchorage independence, and (e) the role of the progression in human cell transformation.

Thus we propose that studies be performed to validate the human cell anchorage independence assay for carcinogens and that the significance of the anchorage-independent phenotype in malignant progressing be determined. Extensive studies using known carcinogens, noncarcinogens, tumor promoters, and cocarcinogens will be done to verify that the anchorage-independent phenotype in human cells is specifically induced by carcinogens. Also, anchorage-independent cells will be characterized to determine the stability and heritability of the phenotype and determine the possible role of anchorage independence in neoplastic progression. The human fibroblast cultures to be used include chemically and radiation-transformed human fibroblasts and apparently normal fibroblasts derived from foreskins.

Stephen Newnow is the project officer.

Staff had proposed a noncompetitive award of this project as a task on an existing Dept. of Energy contract with Northrop Services Inc. The Board decided that it should be competed.

CONCEPT REVIEW FIGURES ARE ESTIMATES ONLY; RFPs, RFAs NOT YET AVAILABLE

The dollar estimates listed 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 projects 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). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

Followup of underground uranium miners. Estimated first year, $100,00, two years.

During the decade beginning with July 1950 medical teams from the U.S. Public Health Service examined 3,362 white and approximately 780 nonwhite males who had worked underground in uranium mines on the Colorado plateau. Occupational medical and smoking histories were obtained during the examinations and often updated during subsequent annual censuses of the miners conducted by the PHS. The white miners now have been followed up through Dec. 31, 1977 using the Social Security Administration, Internal Revenue Service, direct telephoning and other various sources. Sputum samples were also collected from these miners, and cytologic reading performed since 1957.

We are proposing an additional followup of this 4,000 person cohort to obtain vital status information from 1977 and to update their work histories from 1969 (the last time such an exposure update was performed). We plan to merge files currently maintained by NIOSH and NCI, resulting in a file which will include for each member of this cohort, smoking and radiation exposure information, sputum cytologic surveillance information, and the assessment of vital status. For those persons who have died of lung cancer, which at the last followup numbered 200, we intend to review hospital and clinical records in an attempt to obtain an estimate of when these individuals were first diagnosed with lung cancer. This extended followup should help clarify questions concerning the long term health effects of exposure to the current standard of 120 working level months, the interaction between cigarette smoking and radiation exposure as well as the sensitivity and predictive capability of sputum cytologic surveillance of exposed workers.

Thomas Mason and and Philip Prorok of NCI and William Halperin and Robert Roscoe of NIOSH are the project officers.

Application of motivational and job design factors to control carcinogens. Estimated first year, $292,000, three years.

The objective of this project is to devise and evaluate innovative control techniques for use by roofers to reduce their risk of becoming victims of their job hazards. Major hazards of roofing jobs are vapors from asphalts and coal-tar pitches heated for application, dusts of these and other materials generated during roof repair operations, elevated work stations, and steep work surfaces. As a result of these hazards, the more than 100,000 roofers are at increased risk of developing respiratory diseases—lung cancer, emphysema, and asthma, and of being victims of burns, falls, and falling objects.

The purpose of the current project is to apply that proven methodology to a more difficult situation where carcinogens and other serious hazards are known to exist. To meet the objective of this project, the specific aims are: (1) identify and evaluate existing controls, including work practices; (2) develop principles roofers can use for innovating controls, including work practices and job setups, as the work sites dictate; (3) evaluate the effectiveness of the use of the principles in controlling the hazards of roofing work, including exposures to carcinogenic agents; and (4) introduce validated motivational, work practice, and job design principles to the roofing industry.

Robert Mason and Janet Haartz are the project officers.

Assessment of the cocarcinogenic/promoting activity of asphalt fumes. Estimated first year, $208,000, four years.

As a result of a previous NCI-funded NIOSH contract with A.D. Little Inc., asphalt fumes were shown to be carcinogenic by the skin application route. This study on the comparison of coal tar pitch and asphalt fumes found in the roofing industry suggests that risks attributable to each of these materials may be similar, but for different mechanistic reasons. The carcinogenic activity of roofing coal tar pitch fume materials can be attributed, on a first order approximation, to their content of benzo(a)pyrene (B(a)P), which appears to therefore be an excellent indicator substance for assessing exposure. In contrast, the carcinogenic activity of asphalt fumes cannot even approximately be expalined on the basis of their B(a)P) or other polycyclic aromatic hydrocarbon (PAH) content. It is

more likely, based on preliminary chemical analysis, that the carcinogenic activity of asphalt fumes is a result of a low level of initiating activity due to PNA content and to high cocarcinogenic activity where aliphatic straight-chain hydrocarbons account for greater than 99 percent of the condensed fume material.

The proposed study will be an extension of this prior work which will attempt to delineate the active components in the asphalt fumes. Asphalt fumes will be generated in the laboratory, condensed, collected and then separated into two major fractions by extraction and/or chromatography techniques. The aliphatic fraction will be tested by skin application to C3H/HeJ male mice for its cocarcinogenic and promoting potentials using B(a)P at various dose levels as the initiating carcinogen. The PNA fraction will be further separated into three fractions including polycyclic aromatic hydrocarbons and alkylated derivatives, oxygenated PNAs and nitrogen containing compounds. These fractions will be tested for their complete carcinogenic activity and for their initiating potential in combination with the alphatic fraction. Recombination of the complete mixture will also be tested to assure that there are no major losses in preparation of the fractions in comparison to the neat asphalt fume. Appropriate positive and negative controls will be included in the experimental design. Chemical analyses and development of separation techniques will be performed by NIOSH personnel in the Div. of Physical Sciences and Engineering prior to the start of the contract. DPSE will also be responsible for quality assurance of chemical fractions and the routine analysis and characterization of the materials received from the contractor. The study will utilize twice weekly skin application treatments of male mice (singly housed) for a total of 18 months. Detailed histopathologic examination of the treated skin will be the basis for statistical comparisons of tumorigenic potential.

Richard Neimeier is the project officer.

Medical screening in the workplace—a symposium. Estimated cost, $75,000, one year.

Medical screening, part of the continuum of modalities (substitution, engineering controls, environmental monitoring, biological monitoring, medical screening, epidemiologic surveillance) is commonly practiced in industry and recommended by OSHA and/or NIOSH for workers exposed to hundreds of chemical agents. At best, screening may be of real benefit to workers; at worst, it may be a sink for resources that would be better spent on more effective means of prevention.

We propose holding a state of the art conference on medical screening that would address the following areas—characterization of what kind and how much screening in what type of industry; analyses of forces encouraging screening (economic, legal, regulatory, workmens' compensation, etc.); analyses of the goals and underlying tenets of screening programs; critical reviews of screening tests in use in industry (radiography for chest and low back, cytology for sputum and urine, liver function testing, neurological testing, multiphasic testing, and biological monitoring); and analyses of the untoward consequences of screening.

William Halperin of NIOSH and Philip Prorock and Thomas Mason of NCI are the project officers.

Epidemiological assistance for the Div. of Surveillance, Hazard Evaluations and Field Studies of NIOSH. Estimated cost, $250,000, one year.

Within NIOSH, the Div. of Surveillance, Hazard Evaluations & Field Studies conducts epidemiological studies to determine the incidence, prevalence, and resultant disability and/or mortality of acute and chronic disease in the working population. The nature and extent of disease that may be associated with potentially hazardous agents in the work environment are determined by use of coordinated clinical field studies, industrial hygiene field surveys, longitudinal record studies, and surveillance activities.

NIOSH requires services in performing epidemiological data collection and the preparation of the data for analysis. A diversity of skills suitable for conducting epidemiological studies is required. The government intends to satisfy these requirements through issuance of task orders under a basic ordering agreement. During the first year of this contract, NIOSH will require support for five studies.

The purpose of this contract is to obtain epidemiological skills in implementation of specific occupational epidemiology studies. The studies will be based on NIOSH study designs and established procedures. John Whalenof NIOSH and Aaron Blair of NCI are the porject officers.

The Board approved the recompetition of five ongoing contracts totaling nearly $1.6 million in estimated first year awards.

Laboratory rodent and rabbit facility as a resource to the Laboratory of Cellular Carcinogenesis & Tumor Promotion. Present contractor is Microbiological Associates. Estimated first year, $325,000, three years.

Function of this contract is to provide space, care and technical support for the conduct of in vivo experiments. The contractor shall: 1. Provide proper housing and husbandry for the maintenance of healthy intact and nude mice, vitamin-deficient hamsters and normal rabbits. 2. Monitor animal health through periodic testing for pathogenic viruses, bacteria and parasites. 3. Provide a hazard-free environment to safely conduct skin carcinogenesis experiments using initiating and promoting chemicals. 4. Maintain a barrier environment for nu mice to be used for homograft and xenograft experiments a tumorigenicity testing of a vareity of cell lines by injection. 5. Prepare diets for vitamin deficiency studies and monitor animal weights and other clinical signs of deficiency states. 6. Conduct skin painting experiments, including application of chemicals and counting of tumors and gross autopsies. 7. Perform skin grafts on nude mice, inject cell lines subcutaneously and monitor tumor growth. 8. Inoculate rabbits with antigens provided by NCI, bleed inoculated animals and collect antiserum.

Non-SPF rodent holding facility for the Laboratory of Comparative Carcinogenesis. Present contractor is Microbiological Associates. Estimated first year, $325,000, three years.

The present contract was established competitively in 1970 to provide for all DCCP intramural laboratories engaged in carcinogenesis research a long term rodent and rabbit holding facility in which carcinogenesis experiments could be conducted. In accordance with the principle that such resources should be budgeted specifically to the units that benefit from their activities, the current contract was competed and awarded three years ago as a rodent and rabbit resource for Laboratory of Experimental Pathology. Upon establishment of the Laboratory of Comparative Carcinogenesis and the Laboratory of Cellular Carcinogenesis and Tumor Promotion in 1981, the resources of this contract were divided equally between these two laboratories. This recompetition is for that fraction of the current contract that supports LCC activities.

This contract provides a facility for housing all experiments in species, strains or lines of rodents that are not obtainable as SPF products from the FCRF Animal Production Area. These include: chemical carcinogenesis studies such as those in con genic strains of mice that have been developed by Dr. W.P. Rowe (NIAID) to vary in their expression of murine retrovirus coded genetic determinants; transplacental studies in B10.A/J mice, obtainable only from the Jackson Laboratory, that are highly vulnerable to transplacental induction of car-

cinomas of lining epithelia, especially intestinal mucosa; all our studies in Syrian hamsters prior to establishment of an SPF colony of this species at FCRF; and carcinogenesis studies in strains of rats, such as ACI, that are not available at FCRF. Future studies anticipate use of the gerbil, which differs significantly from other rodents in susceptibility to both carcinogens and tumor promoters. The contract will provide for exposing animals to experimental agents, housing them for the duration of each study, performing necropsies, and keeping records. Histology will be done at FCRF and chemistry and pathology at LCC.

J. Ward is the project officer.

Transplacental carcinogenesis and tumor promotion in the patas monkey. Present contractor is Meloy Laboratories. Estimated first year, $250,000, three years.

The current contract at Meloy Laboratories was originally competitively awarded in 1972 and recompeted at three year intervals since then. The closed breeding colony now consists of approximately 185 patas monkeys. The program has successfully demonstrated that the fetal/adult risk ratio is very high in primates for a direct acting chemical carcinogen; that organ specificity is different in the fetus from that in adults; that susceptibility is greatest during the first two thirds of the gestation period, rather than at the end; and that gravid females exposed to at least one chemical carcinogen are at high risk for gestational choriocarcinoma.

Continuation of this project is a major part of the intramural research program of the Laboratory of Comparative Carcinogenesis. Planned future studies are designed to balance short term vs. long term experiments so that the size of the colony remains constant. Long term studies will include continuing observation of carcinogen treated monkeys for tumor development, including more precise definition of periods of maximal susceptibility for direct acting alkylating agents; for metabolism dependent carcinogens that have short lived reactive intermediates; and for metabolism dependent agents that have relatively stable reactive metabolites. The biology of chemically induced gestational choriocarcinoma in this species, the only experimental model for this neoplasm, will be further characterized. The effects of selected compounds known to promote carcinogenesis in rodents will also be evaluated for possible tumor promotion in this primate species, to determine whether the phenomenon occurs and whether target cell specificity will be the same as in rodents.

Short term, chiefly biochemical, studies to complement the in vivo program will include mixed function oxidase induction in fetal and placental tissues and its reversibility or irreversibility (imprinting); DNA repair enzyme activities in fetal and adult target and non target organs; and evaluation of target and non targaet cell responses to tumor promoters.

Animals will be bred, housed, and exposed to experimental substances, and most surgery and necropsies will be performed by the contractor. Histology will be performed at FCRF, and chemistry, pathology, and electron microscopy by LCC.

Amos Palmer is the project officer.

Synthesis of selected chemical carcinogen standards. Present contractors are Midwest Research Institute and SRI International. Estimated first year costs for two awards, $396,000, three years.

Objective of this project is to select a small number of contractors (probably two) with the requisite skills to prepare selelected chemical carcinogens and certain of their derivatives for the Chemical Carcinogen Reference Standard Repository operated under NCI contract at IIT Research Institute. Chemicals stored at the repository are made available to the scientific community upon written request to the Chemical Research Resources Program of the branch.

The derivatives most frequently requiring resynthesis would include epoxides, dihydrodiols, phenols, quinones, and diolepoxides. As is the current practice, compounds requiring resynthesis are flagged by the computer-generated inventory report produced by the repository. With more than one contractor, an equitable assignment of parent hydrocarbons will be made to each laboratory which will have responsibility for preparing derivatives by resynthesis. The assignment of parent hydrocarbons will be designated in the contractor's workscope and will be based on the interest, experience, and capability of the selected contractors together with the objective of establishing a balanced workload distribution among contractors.

In addition to resynthesis work, the contractors will also have primary synthesis responsibility for various classes of carcinogenic compounds which are normally unavailable from commercial chemical supply houses or are not available in sufficient purity. These classes will include nitrosamines, nitrosamides, polynuclear aromatic hydrocarbons, heterocyclic PAHs, aflatoxin metabolites, steroid derivatives, and various compounds with ^{3}H or ^{14}C labeling.

It is estimated that 2½ to 3½ man years/yr effort will be necessary per contractor, and two awards are planned. These incumbent contracts together with the other synthesis contractors and the repository will be introducing a payback system in the near future. It is estimated that the full first year award will be necessary in order to have "up front" money to initiate the work. In future years, it is requested that $150,000 be set aside per year (to cover both awards) as a contingency in case full cost recovery cannot be achieved immediately.

David Longfellow is the project officer.

Survey of compounds which have been tested for carcinogenic activity, 1981-1986. Present contractor is Technical Resources Inc. Estimated cost, $288,000, one year.

Objective of this project is to provide through a searching of the world literature (600-700 journals), a resource document usually referred to as PHS-149, entitled "Survey of Compounds Which Have Been Tested for Carcinogenic Activity."

PHS-149 provides an invaluable resource of a unique nature which is used by many federal and state agencies and by academicians engaged in cancer research and quite specifically carcinogenesis. It augments the IARC monographs and survey bulletins as well as NCI/ NTP Technical Reports and has the virtue of being a condensation of all the world literature presented in a format for easy accessibility and quick review. PHS-149 has been published since 1951. The Report for 1978 was published but there was a lapse from 1973-1977. Surveys are now being prepared for these years. This proposed contract will continue this survey for years 1981-1986.

H.F. Kraybill is the project officer.

NCI CONTRACT AWARDS

Title: Followup of patients on Gastrointestinal Tumor Study Group protocols
Contractor: Mayo Foundation, $87,000.

The Cancer Letter Editor Jerry D. Boyd

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