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DCCP BOARD APPROVES CONCEPTS FOR NEARLY $20 MILLION IN GRANTS, CONTRACTS, INCLUDING NEW INHIBITORS STUDY

A grants program for the study of new natural and synthetic inhibitors of carcinogenesis was given concept approval this week by the Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention. The Board agreed to earmark $1 million for first year funding of the

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In Brief

JOHN CAMPBELL, NIDA CONTRACTS CHIEF, NEW HEAD OF NCI CONTRACTS BRANCH; PHS HONORS SEVEN AT NCI

JOHN CAMPBELL, chief of the Contracts Management Branch at the National Institute on Drug Abuse, has been appointed chief of the NCI Research Contracts Branch. Campbell, 41, was an NCI/RCB staff member from 1973-76. He is a graduate of the Univ. of Tennessee. Campbell will assume his new position later this month, relieving Robert Namovicz, NCI deputy executive officer who has been acting chief of RCB. . . . **SEVEN NCI STAFF** members were recognized for outstanding achievements in the annual Public Health Service Honor Awards made last month. Distinguished service medals went to Director **Vincent DeVita** "For development of curative combinations of anticancer drugs resulting in hope and life for thousands of cancer patients and for decisive leadership of NCI;" and to **Joseph Fraumeni**, director of the Field Studies & Statistics Program in the Div. of Cancer Cause & Prevention, "For outstanding leadership in developing and directing a highly productive program of epidemiologic research designed to clarify the environmental and host determinants of cancer." **Michael Goldrich**, administrative officer of the Div. of Cancer Treatment, received a superior service award "For skillful and innovative administrative management of DCT." **Gilbert Beebe**, an expert with the Clinical Epidemiology Branch, received a special recognition award for his analysis of the health effects of ionizing radiation. Three members of the Div. of Cancer Biology & Diagnosis were honored: **Thomas Waldmann**, chief of the Metabolism Branch, received a distinguished service medal for contributions to the understanding of immune response. **Ira Pastan**, chief of the Laboratory of Molecular Biology, received a meritorious service medal for his work in thyroid biochemistry, gene regulation and molecular mechanisms of malignant transformation. **Gary Peck**, senior investigator in the Dermatology Branch, received a meritorious service medal for "pioneering work" demonstrating effectiveness of retinoid treatment of cystic acne and skin cancer. Not only did DCBD Director Alan Rabson see three of his people honored, he also saw his wife, **Ruth Kirschstein**, director of the National Institute of General Medical Sciences, win the PHS equal opportunity achievement award.

Four DCCP Contracts Costing $9 Million Approved By Board For Recompetition

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DCCP BOARD TABLES STUDY OF MUTAGENS IN HUMAN FOODS, OKAYS RECOMPETITIONS

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grants, which probably will be four year awards.

The DCCP Board also gave concept approval to three new contract supported projects with $1.25 million in estimated first year awards and $4.18 million in total project costs; to the recompetition of four contract supported projects with $2.55 million in estimated first year awards and $8.9 million in total project costs; and to a variety of noncompeting contract programs with an estimated $2 million in first year awards and total project costs of $6.82 million.

The Board tabled a staff proposal for a four year grants program, with an estimated $500,000 a year in awards, to study mutagens in human foods; and deferred a proposal for a noncompetitive one year contract for a study of lung cancer mortality among coke oven workers at an estimated cost of $75,000.

DCCP will issue a request for applications for the natural and synthetic inhibitors study. Carl Smith, program director in the Chemical & Physical Carcinogenesis Branch of the Carcinogenesis Extramural Program, presented the justification for the study:

Epidemiologic studies have implicated diet and nutrition as important factors in the occurrence of human cancer, with both positive and negative correlations indicated for incidence or mortality at many sites with consumption of particular nutrients or food items. High intakes of legumes and cereals such as corn, rice and beans have been associated with reduced risk for breast, colon and prostatic cancers, for example, and an increased consumption of cruciferous vegetables such as cabbage, broccoli, Brussels sprouts and turnips has been associated with decreased cancer frequencies for colon, rectum and bladder. Experimental studies in several animal models have demonstrated in direct feeding studies that certain food or crude food components provide significant protection against chemically induced or radiation induced tumorigenesis. Examples include the cruciferous vegetables, celery, orange oil, beverage sources and edible legumes such as soybeans or soybean concentrates. Diverse types of chemical compounds present in these foods have also been shown to inhibit the neoplastic process, including phenols, coumarins, isothiocyanates, flavonoids and indoles. The extent of occurrence of naturally occurring inhibitors of carcinogenesis, their role and potential as cancer preventive agents, and how protective effects might be enhanced by dietary manipulation are little known at the present time.

Research emphasis in the proposed RFA will seek to expand knowledge and understanding of naturally occurring inhibitors of carcinogenesis and their potential for human cancer prevention. However, it is not the intent of this RFA to stimulate studies on retinoids (including natural vitamin A), vitamins C and E, and selenium; applications dealing with these agents will be considered nonresponsive. Areas for emphasis include:

(1) Identification of new naturally occurring inhibitors with special attention to appropriate methods of isolation of specific constituents or chemical forms; (2) thorough studies on mechanisms of action of newly identified inhibitors and their pharmacokinetics; (3) improvement in current systems for identifying and studying naturally occurring inhibitors; (4) broad determinations of the range of conditions under which efficacy is demonstrable including prevention of carcinogen production or activation, enhancement of detoxification pathways, blocking of ultimate carcinogens, and antipromotion activities. This latter includes dose response studies, species and carcinogen promoters in which efficacy is demonstrable, and potential additive or synergistic effects which may occur by use of more than one agent.

Board member Dietrich Hoffmann commented that a previous RFA on the mechanisms of the biological prevention of cancer brought out "a tremendous response. Not all of the good ones could be funded." DCCP Director Richard Adamson said that those focused on the mechanisms of action and included selenium and vitamins A, C and E, which are excluded from the new RFA.

"The epidemiology is clear," Board member Allan Conney said. "Green and yellow vegetables prevent cancer. The question is, what? Beta carotene and vitamin A are being looked at. What else is important? My feeling is that with cabbage and Brussels sprouts, it may be other things."

"This will elaborate on the search for new test systems," Board member Donald Davies said. "This is breaking new ground."

However, Board member Gilbert Omenn expressed some reservations. "I'm quite unsettled about this. Objective number one is inappropriate. I don't think we should use NCI money to start a far-ranging screening program. That is not the function of the Cancer Institute. The National Toxicology Program would be more appropriate. Also, I'm not aware of information on a large body of work on vitamins A, C and E, or on selenium. The mechanisms are not clear there either. We may be rushing off in search for lesser inhibitors before the mechanisms have been established in the more important ones. . . . If we're going into a drug development program, okay."

"That's not the intent," Adamson said. "This is for the identification of new inhibitors. The Div. of Resources, Centers & Community Activities may set up a rapid screen. We'll stay more with basic mechanisms."

Omenn asked that only those applications which are under the NCI payline be funded, even if it meant that the entire $1 million not be used. Adamson agreed, and the vote to approve the concept was unanimous.

The Board approved NCI's contribution of $500,000 a year to a four year contract administered jointly with the National Institute of Allergy & Infectious Diseases to study the natural history of acquired immune deficiency syndrome in homosexual men. NIAID has committed a total of $2.2 million to the study.

John Cooper, acting director of the Carcinogenesis Extramural Program, presented the staff proposal:

Since June of 1981 investigators have identified an epidemic of acquired immunodeficiency syndrome in the United

States. As of May 9, 1983, 1,410 cases of this syndrome had been reported to the Centers for Disease Control. Although the preponderence of the reports have come from the U.S., an additional 103 cases had been reported from 16 other countries. Since the recognition of this entity, the rise in new cases has been exponential with high case fatality rates within two years of onset. The underlying immune defect in these patients is complicated by the advent of Kaposi's sarcoma, and/or any of a variety of opportunistic infections, the most common of which is pneumocystis carinii pneumonia. Among the U.S. cases, 70 percent have been among homosexual or bisexual males, 17 percent among IV drug users and five percent among Haitians with no history of homosexuality or IV drug use.

The epidemic pattern observed to date suggests an infectious etiology for the underlying syndrome with transmission by sexual contact or by exposure to blood or blood products. The case fatality rate is high, survival after the onset of symptoms is short and no known therapeutic measures have been effective.

Under the circumstances, it would seem prudent to make a serious attempt to collect and store information and material from high risk individuals, which would permit study of the natural history of the disease and the future testing of etiologic hypotheses. Ideally this should be done in a population based manner. Sufficient individuals should be included in the sample so that adequate numbers may fall into various categories: 1) uninfected; 2) infected but without symptoms; 3) infected but with minimal symptomatology; 4) infected with clinically evident disease. Periodic followup and storage of materials would then provide a resource for investigation of both natural history and etiology. Since nothing is presently known with respect to the interval between infection and the development of immune depression, and subsequent OI or KS, it might be advisable to carry out such an activity in two high risk communities, one in which AIDS is presently occurring with high incidence and one where it is now occurring with low incidence.

Concept approval is requested to enter into a collaborative project with the National Institute of Allergy and Infectious Diseases. Funds from this division will be used to supplement the $2,200,000 committed by NIAID in their recently issued RFP (with this title) to increase the magnitude and power of the activities identified. The purpose of this RFP is to establish a sufficiently large cohort of homosexual men at risk of AIDS to study its epidemiology, etiology and natural history. Emphasis will be placed on collecting adequate clinical and epidemiologic data and biologic specimens for future analysis. If only a single technically acceptable response is forthcoming, our assistance would be utilized to expand the size of the cohort to be examined and to increase the frequency of surveillance. If multiple technically acceptable responses are received, an attempt would be made to implement two such activities in communities having high and low current attack rates.

The Board approved the concept of a new project for record linkage studies utilizing resources in population based tumor registries, to be supported through the master agreement mechanism. Under that mechanism, DCCP would identify organizations deemed capable of performing the work, then when specific projects are initiated, RFPs would be circulated only among that group as task orders, with competitive awards to follow.

Board members objected more to the mechanism than to the studies. "I'm not sure we should give you the key to Fort Knox," Board member Carl Shy said, referring to the total project estimated cost of $2.13 million over three years. "I'm not sure we should leave it up to staff to proceed without any further review by an outside review group."

Adamson suggested that approval be given to proceed with the understanding that feasibility studies not to exceed $50,000 each could be undertaken, with proposals for followup substantive studies to be brought back to the Board for concept approval. A total limit of $300,000 was placed on the feasibility studies. The Board agreed.

John Boice, of the Field Studies & Statistics Program, presented the staff proposal:

Population based cancer registries provide unique opportunities to conduct record linkage and feasibility studies of cancer etiology. The existence of records with detailed information on cancer morphology, topography and stage, coupled with the availability of additional detailed information on treatment, occupation and demongraphic characteristics, makes these registries valuable resources for epidemiologic research. The NCI (FSS) currently supports nine such registries in the U.S., and it is frequently recommended that they be used more often for analytical studies. Record linkage studies have been conducted successfully in several registries in the U.S. and around the world, e.g., to study the effects of occupational exposures, drug exposures, and radiation treatment. Such studies are often expanded by abstracting additional information from existing records. This branchwide project would provide managerial, data collection, and processing support to address issues where resources from population based tumor registries could be best utilized. The services would be used for support of collaborative research, including support of investigators in SEER and other population based registries. The contract would be in the form of master agreements where master agreement recipients would compete for awards after a MA order RFP has been issued. It is envisioned that between 15 and 25 national and international cancer registries would compete for these awards.

Because of the large number of cancers reported in population based registries, small effects or rare cancer can be studied effectively by combing results from several registries. In addition, since existing records are already computerized, record linkage studies can usually be conducted efficiently.

Examples of studies to be considered under this project include: (1) The linkage of parental occupation and maternal drug exposure registries to evaluate subsequent childhood cancer in offspring, (2) the linkage of twin registires and cancer registries to evaluate childhood cancer in twins following prenatal x-ray, (3) the linkage of End Results Program and SEER data tapes to determine second breast cancers following radiation treatment for breast cancer (and subsequent record abstraction), (4) the linkage of the Swedish 1960 census data and certain occupational registries with the Swedish Cancer Registry to generate and test hypotheses regarding cancer etiology, (5) the further linkage of data in several cancer registires to evaluate second cancers following radiation treatment for cervical cancer (and additional record abstraction), and (6) the linkage of state unemployment insurance files or other special state occupational rosters with appropriate U.S. tumor registries. It is planned that feasibility studies, generally of minimal expense, would be initiated to determine whether appropriate records can be linked and to evaluate the type and quality of additional data that can be abstracted from existing files. These would then be followed by enhanced studies to obtain detailed information available in hospital and other records. These may be more costly, however, and the Board would be asked to approve any project exceeding $500,000.

The Board approved the concept of a contract for the study of synergistic effects of atmospheric pollutants as environmental carcinogens, at an estimated cost of $50,000 for one year.

The contract would be a joint project with the Environmental Protection Agency. Joellen Lewtas of EPA, the project officer along with Morris Kelsey of NCI, presented the justification:

Polycyclic aromatic hydrocarbons occur to a large extent in our environment, and recent estimates indicate that their production from the combustion of fossil fuels accounts for a majority of the pollutants responsible for the low level (2%) of cancer deaths attributable to "pollution" (Doll and Peto, 1981). Benzo(a)pyrene(BaP) has been used as a general indicator of atmospheric pollution, in the form of PAH, yet reports in the literature estimate that it contributes less than 10 percent of the total carcinogenic activity of automobile exhaust condensates which are a major source of PAH release into urban atmospheres (Grimmer, 1979). Cyclopenteno[cd] pyrene (CPP) has been found to be present at levels higher than BaP in these condensates (Grimmer et al, 1977); Cavalieri et al, 1983), and carcinogenicity tests (mouse skin painting) of CPP have shown it to be a moderately potent skin carcinogen compared to BaP tested in the same system (Cavalieri et al, 1981). Cavalieri (1983) has shown an interesting synergism of BaP and CPP from two-five times that of each alone thus suggesting that these two compounds may account for the majority of mutagenic/carcinogenic activities present in automobile exhaust and certain urban atmospheres. Therefore, further studies are needed to test the significance of these results and hypotheses.

This project would consist of analysis of various ambient air and automobile exhaust condensates for the occurrence and levels of BaP and CPP in order to determine and confirm the higher ratio of CPP to BaP in such samples. Since the EPA has extensive experience in the collection of such samples, they would be asked to become involved in a collaborative effort with the contractor. Newer and more reliable analytical methods will be employed in these analyses since previously published techniques may result in decomposition of the CPP.

Once ratios of CPP and BaP are determined in such environmental samples, it is anticipated that they could be tested both in vitro and in vivo for synergistic effects. Such investigations could be performed by programs within NCI or those of the National Toxicology Program.

The Board gave concept approval to the recompetition of the following contracts for ongoing projects:

Induction, biological markers, and therapy of tumors in primates. Present contractor, Hazleton Laboratories America Inc. Estimated first year award, $550,000, total project, $2.75 million, five years.

Susan Sieber, DCCP deputy director and project officer for the contract, presented the description:

Much in vivo cancer research and a considerable amount of in vitro work utilizes the mouse or other rodent species as the test animal. Rodents are used almost exclusively in the primary screening program designed to identify materials with antitumor effect. Likewise, theyare used extensively to screen compounds for carcinogenic effects. It is evident that many of the basic building blocks for the foundation of cancer research are formulated from rodent data. Unfortunately, there is not good agreement on how accurately rodent data can be extrapolated to man. While it is clearly not feasible to replace rodent studies with studies in nonhuman primates, nevertheless there is a need to utilize nonhuman primates and other animal species more extensively to complement rodent studies and to verify the rodent data by comparative studies in other systems.

This project was initiated in 1961 and until May 1982 was supported by the Div. of Cancer Treatment. On 5/3/82 it was transferred to DCCP with the relocation of the project officer from DCT to DCCP. The present colony, consisting of 484 animals, is comprised of four species: Macaca mulatta (rhesus), Macaca fascicularis (cynomolgus), Cercopithecus aethiops (African green) and Galago crassicaudatus (bushbabies). Seventy-nine of these monkeys are adult breeders whose offspring are used for experimental studies. A total of 28 chemicals have been, or are being evaluated for their carcinogenic potential in lifetime studies in monkeys. The chemicals tested include antibeoplastic and immunosuppressive agents (procarbazine, methylnitrosourea, adriamycin, melphalan, azathioprine and cyclophosphamide), food additives and environmental contaminants (aflatoxin B_1, cycads, sterigmatocystin, cyclamate, saccharin, butter yellow, 3-methyl-DAB, DDT, arsenic and cigarette smoke condensate), "model" rodent carcinogens (urethane, 3-methylcholanthrene, 2-acetylaminofluorene, 2,7-fluorenylenebisacetamide, copper chelate of N-hydroxyacetylaminofluorene, dibenzpyrene and dibenz(a,h) anthracene), and nitroso-compounds (dimethylnitrosamine, diethylnitrosamine, dipropylnitrosamine, 1-nitrosopiperidine and MNNG).

Results acquired over the past 22 years indicate that primates are not as susceptible to chemical carcinogenesis as rodents, that the induction period is often in the range of seven-ten years and that the organ and/or tumor type may differ considerably between rodents and primates for a particular carcinogen. Substances which have carcinogenic activity in some species, usually rodents, but which have not resulted in tumor induction in the course of this study include 3-methylcholanthrene, 2-acetylaminofluorene, 2.7-fluorenylenebisacetaminde, copper chelate of N-hydroxy-acetylaminofluorene, and dibenzpyrene. On the other hand, several chemicals (diethylnitrosamine, dipropylnitrosamine, 1-nitrosopiperidiene, urethane, aflatoxin B_1, cycads and sterigmatocystin) have demonstrated carcinogenic activity in nonhuman primates. Diethylnitrosamine produces hepatocellular carcinoma within two years in essentially 100 percent of exposed animals. Treatment with dipropylnitrosamine, 1-nitrosopiperidine and sterigmatocystin also resulted in the development of primary hepatocellular carcinomas.

Animals exposed to aflatoxin B_1 developed osteosarcomas and tumors of the hepatobiliary system, and treatment with cycads produced a variety of tumors of the liver, pancreas, kidney, esophagus and small intestine. Tumors induced by urethane included brain and intestinal tumors and liver hemangiosarcomas. Cancer chemotherapeutic agents with carcinogenic potential in nonhuman primates are procarbazine, methylnitrosourea and possibly adriamycin. The malignancies induced by procarbazine include acute nonlymphocytic leukemia, osteosarcomas and other solid tumors. Methylnitrosourea administed by the oral route induced squamous cell carcinomas of the esophagus and oropharynx.

The present colony has been in continued existence for 22 years and supports the largest study of chemical carcinogenesis in nonhuman primates undertaken in this country. In addition to providing data on the carcinogenicity of a variety of chemicals, including antitumor and immunosuppressive agents in clinical use, it has also made it possible to acquire information on the spontaneous tumor incidence in nonhuman primates, and their lifespan in captivity. Normal animals of all ages as well as tumor bearing animals have been used in pharmacologic studies and chemotherapeutic trials. The availability of monkeys receiving chronic treatment with chemicals has made it possible to identify some consequences of long term chemical exposures other than tumor development. Monkeys bearing chemically induced hepatocellular carcinomas have been used in studies of AFP synthesis and to cor-

relate serum AFP levels with degree of tumor differentiation and response to therapy. More recently, tumor bearing monkeys have been used to develop new contrast media to enhance computerized tomography of liver and spleen, and to compare the distribution of free and liposome entrapped ara-C in tumor tissue and in adjacent normal tissue. The accumulated experience with specific carcinogens has also made it possible to initiate studies on the prevention or reversal of chemically induced tumors.

This program is designed to study the response of primates to known rodent carcinogens in order to obtain comparative data on susceptibility, latent period, target organ, dose response, and tumor type. It is anticipated that this data, when examined along with other animal data and human epidemiologic data, will allow a more meaningful stepwise extrapolation to man. The low incidence of spontaneous tumors, the long life span, and the phylogenetic position of nonhuman primates makes it possible to perform a number of procedures (sequential laparoscopic examinations, biopsies, diagnostic radiology, bone marrow aspiration, and hematology and clinical chemistry determinations) not readily performed in rodents.

The objectives of the program are as follows: (1) Obtain comparative data on the response of nonhuman primates to known rodent carcinogens and to materials suspected to be carcinogenic in humans; (2) Evaluate the long term effects of antineoplastic agents which are being used clincally for long term remission, in adjuvant therapy, and in the treatment of diffuse collagen disorders; (3) Obtain model tumor systems in nonhuman primates in order to ascertain the potential usefulness of various anticancer agents in man; (4) To try to develop models for chemoprevention therapy; (5) Develop biological markers and diagnostic tests for detecting preneoplastic changes as well as frank neoplasia and for monitoring nonhuman primates and/or patients prior to, during and following therapy; (6) Make available normal and tumor bearing animals for pharmacologic, toxicologic, biochemical, and immunological studies; and (7) Maintain a breeding colony ov various species so that offspring may be readily available for use.

The majority of the animals on this project are housed in an isolated facility which contains only animals committed to this study, and with the exception of the breeding colony, most animals are housed in individual cages. Until 1982, neonates produced by the breeding colony were separated from their mothers at birth and handreared in a nursery. This made it possible to begin dosing with carcinogens during the first few days of life by adding the test compound to the Similac formula at the time of feeding. However, financial considerations have recently made it necessary to allow the offspring to remain with their mothers until weaning. Test compounds are given subcutaneously, intravenously, intraperitoneally or orally. The dose level chosen is dependent on the chemical under evaluation. Antineoplastic and immunosuppressive agents are administered at doses likely to be encountered in a clinical situation; other substances, such as environmental contaminants, are given at levels 10-40 fold higher than the estimated human exposure level. The remainder of the chemicals tested are administered at maximally tolerated doses which, on the basis of weight gain, blood chemistry and hematology findings, and clinical observations, appear to be devoid of acute toxicity. Dosing continues until a tumor is diagnosed or until a predetermined exposure period has been completed.

A variety of clinical, biochemical and hematological parameters are monitored weekly or monthly, not only to evaluate the general health status of each animal, but also for the early detection of tumors. A laparoscope is used to periodically examine the abdominal cavity, mainly the liver, for evidence of tumor. Surgical biopsies are obtained when indicated and submitted to NCI for histopathological evaluation. Surgical procedures are performed under Ketamine hydrochloride or sodium pentobarbital anesthesia. All animals which die or are sacrificed are carefully necropsied and the tissues subjected to histopathologic examination.

Animals are bred, housed and dosed with test chemicals by the contractor. Surgery, biopsies and other procedures are performed jointly by the project officer and the contractor. The project officer provides the contractor with written protocols for all experimental studies. Test materials are prepared by NIH personnel and all monkeys are necropsied at NIH.

"To show that a rodent carcinogen is not necessarily a primate carcinogen is a fascinating piece of information," Board member Renato Dulbecco commented.

Board member Hilary Koprowski suggested that the animals would be useful to investigators for other purposes, especially in studying effects of drugs on brain tumors. "The blood-brain barrier is pure theory," Koprowski said. "Your animals could be extremely important in studying that issue."

Sieber said she would be willing to consider that suggestion.

Adamson referred to the lack of mammary cancers and the overall lack of spontaneous tumors in primates, which he said possibly could be attributed to low amounts of fat in their diets. DCCP is considering manipulating the diets of some, "maybe feeding them hamburgers," and another group hamburgers along with cruciferous vegetables, "and see what happens."

Omenn mentioned "the elaborate setup of seven or eight primate centers around the country. Are any of those people knowledgeable about primates involved (in the NCI project)? This is too valuable a resource to keep within NCI."

"We have approached other primate centers. They have not been too interested, other than in use for breeding," Adamson said.

"Things may have changed," Omenn said.

Adamson said that he plans to "let it be known what we have available."

"I think you should take advantage of the expertise around this table," Board member Edward Bresnick said.

"I don't have any problem with building that into the RFP," Adamson said.

Resource to support the chemical, economic and biological information needs of DCCP and to provide chemical process, production and economic information as support to IARC. Present contractor, SRI International. Estimated first year award, $700,000; total cost, $2.1 million, for three years.

Herman Kraybill, DCCP scientific coordinator for Environmental Cancer, presented the project description:

The objective of this project is to provide a mechanism for the development of information and data in the areas of environmental and occupational cancer. The project, which was initiated eight years ago and was recompeted about four years ago with the awarding of a new contract beginning in October 1979, consists of four major tasks. The first task has been to support the efforts of NCI's Chemical Selection Working Group (CSWG) to select and nominate chemicals for carcinogenicity bioassay. NCI, and this division in particular, have

been and will continue to be, the primary source for nomination of candidate chemicals to the National Toxicology Program for carcinogenicity testing (formerly the sole responsibility of this Institute). This task involves conduct of class studies (chemicals by use and structure classes). During the past three years (FY79-81), 12 class studies were completed; two class studies are currently in progress. From such class studies and other information sources, summary sheets are prepared which the CSWG uses in the selection and monination process. In addition to being a source for nomination, these class studies are published in the open literature. Additionally, IARC monograph reviews and random nominations (i.e., nominations from sources other than class studies) serve as sources of summary sheet preparation. In the past three years, 131 summary sheets (106 from class studies and IARC monograph reviews and 25 from random sources) have been prepared. Also, results from two contracts on short term testing, administered by this Division and up for concept review at this meeting, are incorporated into the summary sheets.

In the second task, the project provides support to IARC (International Agency for Research on Cancer), Lyon, France. It involves submission to IARC of data contained in the first section of each monograph, such as chemical and physical data, production and exposure data, and analytical methods. In the last three years such data were furnished on 146 chemicals at 12 working group meetings in Lyon. Additional information for 35 chemicals and a data table for 275 rubber processing chemicals were provided.

In the third task, major emphasis is on the development of data and information for the Chemical Carcinogenesis Research Information System. This data base has become quite significant. It contains compilations of data on carcinogens, mutagens,a dn tumor promoters and cocarcinogens. There is also a limited amount of data on chemicals which were tested for carcinogenicity and yielded negative results. The data is routinely stored in PROPHET, an NIH supported time sharing computer system specifically designed to meet the data analysis needs of scientists involved in biomedical and pharmcological research. More recently, the data base has been entered into CIS (Chemical Information System), a multi-agency system, cosponsored by NIH, which is a publicly accessible system used on a fee for service basis by some 1,400 users in 30 countries. For chemicals tested for carcinogenicity, there are data for 473 chemicals (369 chemicals with positive results, 104 chemicals with negative results, and a total of 1,552 test results.) The mutagenicity data base contains information on 465 unique chemicals (308 chemicals tested in the Ames assay, 87 by E. coli WP2 test system, 16 by Chinese hamster ovary cell HGPRT locus (CHO/HGPRT), 112 by Chinese hamster V-79 cell assay and 16 for mouse lymphoma cell L5178Y ($TK^{+/-}$) assay), for a total of 1,137 test results.

Data are being accumulated on mammalian cell transformation and other cell systems. Thus far, there is information on 89 tumor promoters and cocarcinogens (115 test results). These figures are as of November 1982. All CCRIS data resulted from a search of epidemiological and animal evidence; from NCI/NTP technical reports, IARC monographs, NCI/contractor studies on water and air pollutants, NCI/contractor class studies previously mentioned under Task I, and reviews and surveillance of literature. Another function of this task is the development of the Bioassay Report Summary Handbook, a most useful reference source on 215 chemicals, as of this date. This handbook contains summaries of the NCI/NTP technical reports from the bioassay program and will be continually updated as will the data bases referred to above, including the short term test program data base.

Finally, the fourth task relates to research and developments that will yield data for some of the foregoing data bases plus new data bases that can be utilzed in production of ready reference sources (hard copy) and for introduction into online searchable data resources. Special research tasks in the past and in progress include (a) lists of organic and inorganic contaminants in drinking water evaluated for carcinogenicity and mutagenicity, also promoters and/or cocarcinogens and, where indicated, monographs on each of these chemicals; (b) study of air pollutants, identification and classification as to carcinogenicity, mutagenicity and also listing of promoters and/or cocarcinogens; (c) a survey of environmental monitoring data; (d) species to species comparison of metabolism, a listing of significant metabolites; (e) a study on metal containing drugs; and (f) an abridged listing of chemicals that are currently recognized as inhibitors of carcinogenesis. Also, this task provides for review, editing, and ultimately, the publication of aforementioned class studies and special studies reports in the open literature for use by the scientific community at large. Tasks relating to chemical selection included (a) selection and ordering of classes for study, (b) significance of in vitro tests in chemical selections; (c) development of summary sheet format and content; and (d) chemical selection of lists of promoters and cocarcinogens.

The current contract project is funded through Sept. 29, 1984. It is the intention of DCCP to carry forward the four tasks. It is proposed that the contract project covers three years, on a competitive type award, at the same level of funding as proposed for the first year.

For Task I it is planned to have the same level of financial support as in the current contract on the assumption that the nomination and selection process will continue at the present rate of 15 nominations per year. In the event that the testing program will start testing more chemicals for carcinogenicity (i.e., 30) then some future adjustments will have to be made. As it stands now, it is anticipated that in the three year period of performance this will involve approximately 10 class studies (depending on the size and scope), about 45 summary sheets, and nominations for short term studies at the rate of 70-90.

For Task II involving IARC support, the same level of effort is anticipated in the future three year performance period. It is expected that for nine meetings (three meetings per year) physical and chemical data, production and exposure values, and analytical data will have to be provided on approximately 225-270 chemicals (75-90 chemicals per year).

For Task III the current mechanism set up for securing information and data for the Chemical Carcinogenesis Research Information System will be continued. We anticipate evaluation of approximately 450 chemicals for classification as carcinogens and about 1,000-1,500 for classification and identification and identification as mutagens. For the Bioassay Report Summary Handbook we expect compilation and addition of 52 new summaries per year for a total of 156 for the three year contract period. Additionally, data will be added to CCRIS from special studies developed under Task IV. We do not have a precise estimate at this time but from past experience, assuming three to four special studies per year with a yield of information on about 50 chemicals (eliminating duplications), one could expect total input into CCRIS on approximately 600 chemicals. Information from the short term testing program should come from testing of at least 150 chemicals in three years. With the progression of exploratory sub-tasks under Task IV, more data will be entered on promoters, cocarcinogens and inhibitors.

Task IV is the foundation for research and development on mechanisms and resources for securing information that is used in identification and classification of carcinogens, mutagens, promoters, cocarcinogens, inhibitors, and their metabolites that are in the environment. The information and data developed therefrom are published as special government reports or in review articles in the open literature and are ultim-

ately incorporated into CCRIS. While these data bases are of great use to NCI, they are also widely used by other agencies, academia, nonprofit research foundations and industry. They have been utilized, for example, in the preparation of position papers and presentations at scientific meetings such as organic pollutants identified in air and drinking water. We expect at least three special studies per year, or for the three year period of this proposed contract, a total of nine or 10 such studies. In order to be able to be responsive to current issues, it may not be prudent to get locked in on specific studies for the three year performance period, but studies may be indicated on carcinogens and mutagens occurring in natural products; specification and/or identification and classification of natural chemical inhibitors in foods and diet (carrots, Brussels sprouts, garlic, etc.), effects of thermal and radiation processing on formation of carcinogens and mutagens in food; survey of carcinogens, mutagens and promoters in excretory products (feces and urine); and survey and identification of contaminant chemical exposures that may be associated with potential carcinogenic effects.

Encompassed under Task IV is also the publication of class studies and special studies reports. With the continuous development of class studies, the division decided some time ago that this important resource should be published. Therefore, some effort is needed to edit and prepare in final form for publication the class studies and special reports accomplished under this task.

"What would happen if you did not have this contract?" Omenn asked.

"You would get a Chevrolet instead of a Buick." Kraybill answered. "Fewer chemicals nominated, less information about them."

"NCI nominees have the best information of those submitted to NTP," Adamson said. This includes biological, exposure, and production data.

"How many NTP chemicals selected for testing are NCI nominees?" Omenn asked.

"The greater majority," Adamson said. "Ninety-three percent," Kraybill said.

"Why make this competitive?" Hoffmann asked. "No one else can do this."

"Yes they can," Adamson said. "Anyone can come in and compete for it. We've seen some interest by other organizations. We're not wedded to SRI."

Kraybill pointed out that in the previous competition for the contract, five organizations submitted proposals.

Omenn offered the motion to approve the concept, commenting, "To make any further cuts I don't feel would be advisable."

Biomedical computer support services. Present contractor, ORI Inc. Estimated first year award, $1.05 million; total cost, $3.3 million over three years.

Michael Stump presented the project description:

This is a support services contract for the Biometry Branch. Services are provided to the Office of the Chief, the Biometric Research & Analytical Studies Section, the Demographic Analysis Section, and the Computer Science Section. Services provided under this contract include computer programming, computer systems analysis, technical documentation, operation of the Landow remote terminal facility, and clerical support related to computer applications.

The level of effort for this contract is currently 26 persons and expected to remain at this level throughout the course of the contract. The Biometry Branch has relied on support contracts for a majority of its computer related service needs since 1970. The primary reason for using a contractor in lieu of inhouse resources is the variability of computer support requirements from year to year. The concept of contracting for these types of services was reviewed and approved by the DCCP Board of Scientific Counselors in February, 1982.

Contractor services are provided by an organized team of computer project managers, computer professionals, and support personnel. The contract is administered by the Computer Science Section. The contractor's project manager and the NCI project officers jointly allocate contract resources in accordance with Biometry Branch priorities and needs. End projects are comptuer programs and systems, technical documentation, computer output such as listings, tables, and graphs, and services such as data entry (keying).

A partial list of Biometry Branch projects receiving support from this contract includes: 1) Development of a user oriented software package for the analysis of incidence and mortality data; 2) Editing, correcting and tabulating incoming data from SEER registries; 3) Development of a prototype data management system for SEER registries; 4) Systems development for data collection and analysis of a followup study of survivors of cancer in childhood and adolescence.

In vitro evaluation of chemical candidates for in vivo testing. Present contractors are Microbiological Associates, whose contract is being recompeted for three years with an estimated first year award of $185,000 and total cost of $577,000; and Research Triangle Institute, whose contract is being recompeted for three years with an estimated first year award of $62,400 and total cost of $195,000.

Thomas Cameron, DCCP assistant scientific coordinator for environmental cancer, presented the project description:

In March 1981 two contracts (Ames salmonella typhimurium and mouse lymphoma L5178Y $TK^{+/-}$) were competitively awarded to aid the Office of the Scientific Coordinator for Environmental Cancer in its support of intramural and extramural activitieis of the division. The primary thrust of the contracts was to fill gaps in knowledge in mutagenicity data needed to select NCI nominations for carcinogenicity testing in the National Toxicology Program. To comply with the mission of NCI and of this division's role in identifying etiological factors of cancer, we have been and will continue to be the major source of nominations to that multi-agency activity. A format has evolved to look at large groupings of chemicals (by chemical classs or use category) in order to systematically select the best candidates. This has routinely shown the paucity of in vitro data on most of the compounds. Data obtained in these mutagenicity assays have provided information to the selection group, enabling them to make informed choices in a timely fashion.

Other applications of these contract activities have developed as individuals and organizations have learned of their availability. One example concerned the initial tentative association of amyl nitrate usage with the occurrence of acquired immune deficiency syndrome in a certain population subset—that compound and four closely related compounds were tested, at the request of the Field Studies group and the NTP, to supply additional biological information for opinions and actions they were formulating. Likewise, in a cooperative effort with the Bureau of Foods, FDA, seven compounds containing the cinnamyl radical were tested because that moiety had been a part of a food additive positive in a chronic rodent bioassay. Our results completely confirmed those previously obtained in the FDA laboratory, and will permit them to move forward with confidence. Limited positive bioassay findings released by the Frederick Cancer Research Facility, supplemented by positive findings from our contracts, have

convinced private industry to investigate thoroughly a major chemical.

In the two years that these contracts have been in operation 110 compounds have been identified for study and are in various stages; i.e., being procured, on test, or reported out. Over 60 compounds have been completed in both assays, and we are presently analysing those reports. In addition to reporting the results to those groups and individuals who initiated the original request, we are preparing a series of manuscripts presenting the results as a consequence of chemical structure or by chemical usage as appropriate. The initial manuscripts will be on five sulfur containing heterocyclics and seven cinnamaldehyde analogs; papers on a group of metallic inorganics and some 16 dyes and dye intermediates will follow. Correlations will be made between the two assays as well as references found in the open literature and to reports available from other laboratories. This is an excellent opportunity to correlate findings between assay systems and between laboratories under well controlled conditions, and will add to the government and private sector activities that are presently evaluating many of the assays available either commercially or as developmental projects.

In order to continue this support to intramural and extramural activities of this division, approval is requested to initiate a competitive renewal of contracts for these assays—the Ames Salmonella typhimurium and the mouse lymphoma —for the purpose of awarding three year contracts for each. The present contracts call for a maximum of 75 compounds a year to be tested in each assay and the capability to repeat 25 of those tests in the event of equivocal results. The chemical selection activity of the NCI has been moderately reduced to conform with the anticipated chronic rodent bioassay component of the NTP; consequently, it is no longer necessary to continue at the present level. It is estimated that a reduction by 40 percent—down to 45 initial tests and the provision for 15 retests—would be adequate in the foreseeable future.

The proposed workscopes for the renewed contracts will duplicate those presently in effect. Each compound will be tested in five tester strains of Salmonella typhimurium both with and without S-9 activating systems derived from both rat and hamster liver. Each test will have five dose levels determined by prior range finding tests, and will incorporate designated positive as well as solvent or negative controls. In the mouse lymphoma assay five doses selected on the basis of cytotoxicity will be tested both with and without metabolic activation. Appropriate positive and solvent or negative controls will also be included in each assay.

Test compounds will be procured through another contract (the chemical procurement and repository activity presently under contract to DCCP) and aliquot portions will then be supplied to each laboratory conducting the assays. Chemicals are acquired by the repository on an as needed basis and in sufficient quantity (usually 30 grams) to permit repository to retain a like or greater amount for future reference or to resupply the laboratories if additional compound is required for retest.

Each individual chemical shipment sent from the procurement source to the laboratories is identified by a code number and is accompnaied with instructions as to the correct solvent to use; i.e., water, DMSO, ethanol, or acetone. Both laboratories have been instructed to coordinate their purchase of solvents so that they use the identical supplier batch as designated by lot number. In addition, each chemical shipped is accompanied by a sealed envelope, addressed to the safety officer specified by the laboratory, containing the available information on toxicity, neutralization, cleanup procedures, etc., to be opened only in the event of an accident with that particular compound. When the test is completed, if the envelope has not been opened because of an emergency, it is returned unopened to the project officer. Each laboratory shall prepare two reports on each compound—a brief narrative and completed computer forms for input to a data bank for the use of government agencies.

The proposal for a study of mutagens in human food was tabled following opposition by Omenn, Hoffman and Conney.

"We don't have a single animal model to show that these mutagens cause digestive tract or tracheal tumors," Hoffmann said. "Before we spend $2 million on this, wait until we do."

"This is not suitable for a directed effort," Omenn said. He suggested that rather than issue an RFA or RFP, NCI should publish the proceedings of a recent workshop on mutagens in food and mention interest in supporting grants in that area.

"We could put out a program announcement," Adamson said.

"No, not even that," Omenn insisted.

Adamson suggested that the workshop be published, "wait 18 months, and if nothing comes in, we could then have a program announcement." Program announcements indicate NCI's interest in a subject area but do not reserve any money to fund those grants; they must compete in the regular R01 or P01 pools.

"We had a program announcement several years ago on mutagens, and it failed miserably," David Longfellow, assistant chief of the Chemical & Physical Carcinogenesis Branch, said. "They did not fare well in the study sections."

Board Chairman Peter Magee suggested that the concept be tabled until after Board members have an opportunity to read the proceedings of the workshop or a summary to be provided them. The Board agreed.

The lung cancer-coke oven workers study was to have involved a contract with the Univ. of Pittsburgh to combine and organize data in its possession on steel workers. Board members objected to what they said was an inadequate description of the concept. It was deferred with the suggestion that it be resubmitted with a more complete presentation.

The noncompetitive contract concepts approved by the Board will appear next week in ***The Cancer Letter.)***

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