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NTP COMMITTEE ACCEPTS INDUSTRY POSITION ON POLICY TO SEPARATE FIGURES FOR BENIGN, MALIGNANT LESIONS

The Technical Report Review Committee of the National Toxicology Program's Board of Scientific Counselors has agreed to what could be a precedent setting policy which could influence interpretation of carcinogenesis bioassay results and subsequent regulatory actions.

The committee agreed that technical reports should clearly separate

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In Brief

CHEMICAL CARCINOGENESIS, EPIDEMIOLOGY TRAIL VIRAL ONCOLOGY IN BUDGET GROWTH, BOARD NOTES

"IT'S SAD to see the slow growth in biometry and epidemiology," Brian Henderson commented at a meeting of the Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention. The Board was discussing the DCCP budget, and Henderson noted that biological carcinogenesis—"that's really viral oncology"—was still growing. "Study sections are saying grants in the biological carcinogenesis area have higher priority scores," DCCP Acting Director Richard Adamson said. "If we take the advice of study sections, and everyone says we should, we have to fund them. If you are suggesting that we skip over priority scores to fund other areas, the National Cancer Advisory Board has to deal with that." Responded Board member James Watson, "We should oppose going against the study section recommendations;" Charlotte Friend agreed. But, after DCCP Administrative Officer Steve Ficca pointed out that funds could be reserved for specific areas through RFA announcements, Bernard Weinstein said, "It is clear that if you really want to do more in chemical carcinogenesis and epidemiology, we're not doing it." Board Chairman Peter Magee said, "Unless funds are made available, younger investigators will not be attracted into those fields." . . . **R. LEE CLARK**, president emeritus of the Univ. of Texas System Cancer Center, has been appointed UT System professor of surgery and oncology by the Board of Regents, only the third time the regents have approved a systemwide professorship. Other awards and appointments at UTSCC/M.D. Anderson: **GARTH NICOLSON**, who heads M.D. Anderson's new Dept. of Tumor Biology, has been appointed to a new professorship in cancer research; **JOSEPH BURCHENAL**, director of clinical investigation at Memorial Sloan-Kettering, was the Jeffrey A. Gottlieb Memorial Lecturer this week; **PHIL GOLD**, the Canadian who discovered CEA, received the annual Heath Memorial Award; and **BASIL MORSON**, director of research at St. Mark's Hospital in London, received the Joanne Vandenberge Hill Award. . . . **DOUGLAS CRAIG** has been appointed director of toxicology for Litton Bionetics.

NTP COMMITTEE DECISION SAID LEANING TOWARD INDUSTRY POSITION ON REPORTS

(Continued from page 1)

the reporting of benign tumors from malignancies attributed to compounds tested. The practice in the Carcinogenesis Testing Program has been to include them together in weighing the evidence against a substance. Spokesmen for industry have argued for such a separation, but without success until the committee's meeting last month to review bioassay reports.

The issue was raised by James Swenberg, chief of pathology for CIIT, one of the industry representatives on the committee. The draft report on the bioassay of di(2-ethylhexyl) phthalate, the most commonly used plasticizer for polyvinylchloride polymers, was being reviewed. The report summary noted:

"Hepatocellular carcinomas or neoplastic nodules in high dose rats of either sex and in low dose females, and hepatocellular carcinomas or adenomas in low and high dose mice of either sex occurred at incidences significantly higher than those in matched controls. . . . Under the conditions of this bioassay, [the compound] was carcinogenic for F344 rats and B6C3F1 mice of either sex, causing increased incidences of hepatocellular carcinomas or neoplastic nodules in rats and hepatocellular carcinomas or adenomas in mice."

Svend Nielsen, pathology professor at the Univ. of Connecticut, was the committee's primary reviewer of the report and Norman Breslow, professor of statistics at the Univ. of Washington, the secondary reviewer. Both agreed with the conclusion of the report. "There is clear evidence of carcinogenicity in mice and rats," Breslow said. "In terms of human risk, it is a potential risk to man, although that requires wider analysis beyond the purview of the report."

"I seriously question the validity of lumping hepatic carcinoma with neoplastic nodules in determining carcinogenesis," Swenberg said. "Some nodules may proceed to malignancy, but some regress."

Committee Chairman Margaret Hitchcock pointed out that the tables in the body of the report separated the two, and that it was in the summary where they were grouped together.

Norton Nelson, chairman of the NTP Board of Scientific Counselors, agreed that "It would be a mistake to blur the distinction between the two. But it is important to note the biological significance. The nodules are undoubtedly a precursor, but that's a subjective conclusion."

"Fifteen percent of those who get hepatic adenoma die from what is essentially a benign disease. It's a serious lesion," NTP Director David Rall said.

The committee approved the report, with some minor modifications in addition to language separating carcinomas and neoplastic nodules. The issue came up again in reviewing the report on the bioassay of 11-aminoundecanoic acid, a monomer used for the production of nylon 11. The summary of that report said:

"Hepatocellular adenomas, carcinomas, or neoplastic nodules, and transitional cell carcinomas of the urinary bladder (a rare tumor in F344 rats) occurred at incidences significantly higher in high dose male rats than in the controls. Hyperplasias of the transitional epithelium of the kidney and bladder of rats of either sex and renal atrophy and mineralization in the kidney, lung and glandular stomach of mice were also associated with administration of 11-aminoundecanoic acid. A moderate increase in malignant lymphmas was found in low dose male mice. No increase was observed in the high dose group; however, significantly reduced survival may have negatively biased the incidence of this age related neoplasm. Under the conditions of the bioassay, [the compound] was carcinogenic for male F344 rats, causing significantly increased incidences of hepatocellular adenomas, carcinomas, or neoplastic nodules and transitional cell carcinomas of the urinary bladder. It was not carcinogenic for female F344 rats or for B6C3F1 mice of either sex."

Swenberg objected again to including nodules with carcinomas, along with other "significant deficiencies . . . Additional studies are needed to assess carcinogenicity. The correct conclusion should state that 11-aminoundecanoic acid may pose a carcinogenic hazard when administered in doses that produce hepatotoxicity."

The primary reviewer of the report, Swenberg asked that it be rewritten to include a statement that only the nodules were produced in some animals, that in one section references to hepatic carcinoma be deleted, and that no estimate for human risk be included.

"This committee is not the best group to resolve the differences on nodules," said Frank Mirer, organized labor (United Auto Workers) representative on the group. He agreed that there were some deficiencies in the study, but that there were indications that the compound was not adequately tested. "I think this compound presents human risk of unknown magnitude."

Incidence of malignancies in "published historical controls exceeds that in the tested animals," Swenberg argued. "Throughout the report, carcinomas and adenomas are lumped with nodules, when the increased incidence was only in nodules."

Jack Moore, NTP deputy director, pointed out that bladder tumors almost never are seen in controls. Swenberg agreed "there is clear evidence this compound is inducing bladder carcinoma."

The committee approved Swenberg's motion to re-

ject the report and return it to NTP for "appropriate rewriting and updating of some tables."

Grouping neoplastic nodules with carcinomas frequently makes the incidence of chemically induced lesions statistically significant. Not doing so "is an industry position," one observer told ***The Cancer Letter.*** "It lessens the significance of benign lesions found in dosed animals, and makes the regulatory process more difficult."

Other bioassay reports reviewed by the committee were:

C.I. acid orange 10. A textile dye. "In male rats, the incidences of neoplastic nodules of the liver in high dose group and mesotheliomas of the tunica vaginalis in the low dose group were significantly higher than those in the controls, but the levels of significance did not meet the Bonferroni inequality criterion. No compound related neoplastic or nonneoplastic lesions were observed in the female rats or in mice of either sex. It was concluded that, under the conditions of this bioassay and at the dose levels tested, C. I. acid orange 10 was not carcinogenic for male or female F344 rats or for male or female B6C3F1 mice."

While not disagreeing with the conclusion, the committee approved Nielsen's motion to return the report to NTP for clarification of some aspects and additional information, the second time the committee had returned the report for revisions.

Bisphenol A. An intermediate used in the manufacture of epoxy, polycarbonate, and polyester styrene resins. "Leukemias occurred in high dose male rats and low dose male mice at incidences significantly higher than those in the controls, but in both instances the levels of significance were above those required by the Bonferroni inequality criterion. A compound related increased incidence of multinucleated giant hepatocytes was also observed in male mice. Under the conditions of this bioassay, bisphenol A was not carcinogenic for F344 rats or B6C3F1 mice."

The report was accepted, with some revisions, although Mirer said, "I would hesitate to make the statement, in light of the hematopoietic data, that it is not carcinogenic."

C.I. acid red 14. A textile dye. "Sebaceous adenomas of the clitoral gland in high dose female rats were observed at an incidence significantly higher than that of the matched controls, but the Bonferroni inequality criterion for comparing two dosed groups with a common control was not met and when the incidences of animals with sebaceous adenomas or squamous cell carcinomas were combined, the results of the Fisher exact test were not significant. Endometrial stromal polyps of the uterus were observed in high dose female rats at an incidence significantly higher than that seen in the matched controls. However, since this tumor type has occurred in a group of control female rats at the same laboratory at an incidence exceeding that observed in this study, the association between the increased incidence of endometrial stromal polyps and administration of C.I. acid red 14 is not clearly established. [The compound] was not associated with an increased incidence of any tumor type in mice. [It] was not carcinogenic for F344 or B6C3F1 mice of either sex under the conditions of this bioassay."

Breslow's motion to accept the report and summary, but with the statement that "there is no conclusive evidence on possible carcinogenicity to humans," was approved.

2,6-dichloro-p-phenulenediamine. A chemical intermediate. "Hepatocellular carcinomas or adenomas occurred in high dose mice of either sex at incidences significantly higher than those in the corresponding controls. Ectopic hepatocytes were observed at an increased incidence in the pancreas and nephrosis was observed in increased severity in dosed rats of either sex when compared with the corresponding controls. Under the conditions of this bioassay, [the compound] was carcinogenic for B6C3F1 mice of either sex, causing increased incidences of hepatocellular adenomas and carcinomas. It was not carcinogenic for F344 rats under the conditions of the bioassay."

Sheldon Murphy, Univ. of Texas (Houston), was the committee's primary reviewer of this report. He said he agreed with it, but that the conclusions needed restating. "The malignant tumors, taken by themselves, were not statistically significant." His motion that the hepatic carcinomas be shown separately from the adenomas, following the policy adopted previously, was approved unanimously.

Locust bean gum. A widely used food stabilizer. "Although alveolar/bronchiolar adenomas occurred in low dose male mice at a significantly higher incidence than that in the matched controls, no significant statistical results were obtained when the incidence of animals with adenomas or carcinomas was analyzed. It was concluded that under the conditions of this bioassay locust bean gum was not carcinogenic for male or female F344 rats or B6C3F1 mice."

Roy Shore, New York Univ., the committee's prime reviewer of this report, agreed with the conclusion but said, "Because of the maximum tolerated dose, the test was not adequate or definitive." His motion to accept the report was approved.

NTP BOARD CONSIDERS MODIFICATION OF HUMAN RISK STATEMENT IN REPORTS

Every report on a bioassay completed by the Carcinogenesis Testing Program—when that program was in NCI and now in the National Toxicology Program—includes the following statement as part of the foreword:

"This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a greater inci-

dence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical could pose a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study."

The NTP Board of Scientific Counselors and its Technical Report Review Committee had expressed concern about that statement; some felt that a statement on human risk should be more explicit. NTP Director David Rall presented some alternatives.

Rall noted that the International Agency for Research on Cancer offers assessments of the strength of evidence for carcinogenicity from experimental animal studies which are presented in one of four categories—sufficient evidence, limited evidence, inadequate evidence, and negative evidence. They are defined as:

- Sufficient evidence of carcinogenicity indicates that there is an increased incidence of malignant tumors in multiple species or strains; or in multiple experiments (preferably with different routes of administration or using different dose levels); or to an unusual degree with regard to incidence, site or type of tumor, or precocity of onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.
- Limited evidence of carcinogenicity means that the data suggest a carcinogenic effect but are limited because the studies involve a single species, strain, or experiment; or the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of followup, poor survival, too few animals, or inadequate reporting; or the neoplasms produced often occur spontaneously or are difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumors in mice).
- Inadequate evidence indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.
- Negative evidence means that within the limits of the tests used, the chemical is not carcinogenic.

The categories 'sufficient evidence' and 'limited evidence' refer only to the strength of the experimental evidence that these chemicars are (or are not) carcinogenic and not to the extent of their carcinogenic activity or potency. For chemicals having 'sufficient evidence of carcinogenicity in animals,' the IARC makes the following statement: "In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals (or the particular chemical name) as if they (it) presented a carcinogenic risk to humans."

Richard Griesemer, former director of the Carcinogenesis Testing Program, and Cipriano Cueto, former chief of the program's Toxicology Branch, examined 198 NCI bioassays and expanded the IARC categories—very strong evidence for carcinogenicity in two species; very strong evidence in one species and sufficient evidence in a second species; very strong evidence in one species and no evidence in a second species; equivocal evidence for carcinogenicity in one or two species; no evidence in limited animal experiments; no evidence in one species; no evidence in two species.

Rall suggested that the Board consider continuing with the statement now in the foreword, with more specific remarks elsewhere in the report when appropriate. One alternative, Rall said, would be an array of comments patterned after the Griesemer-Cueto categories, or go with the IARC definitions. Rall suggested this paraphrase of the IARC statement:

"The NTP peer review panel considers the results of this bioassay as being sufficient evidence for the carcinogenicity of (chemical name) in rats and mice (or whatever experimental animals). Moreover, in the absence of adequate data in humans (if that is the case), the panel believes that (chemical) should be regarded as presenting a carcinogenic risk to humans."

Board Chairman Norton Nelson commented that quantitative risk assessment is a concern of several groups and "there are proposals floating around Washington and the rest of the country." The Environmental Protection Agency is attempting to develop criteria. "There is a fair amount of emotion regarding turf rights. Some agencies want to do their own. My concern is that this Board not get into quantitative assessment now. Perhaps that is a cop out, but I think we shouldn't get ourselves in a national debate."

Nelson agreed that the reports should include some reference to human risk. "Something like, this information is a warning. Animal data means something. Something like that needs to be said. We should choose words that are a warning."

Nelson said the level of detail in the Griesemer-Cueto approach "is not helpful. These are things said in the summary statement (where study results are described). We do not want to enshrine them in gold."

Board member Marjorie Horning said, "When we identify a chemical as a carcinogen, we have to say where one is a much greater risk than others. What is the bottom line?"

"There are several bottom lines," Nelson said. "The real bottom line is when agency X decides to regulate or not. How much exposure to permit. The Delaney amendment permits no exposure at all. We

have to educate ourselves on how far to carry this procedure. We can't tell Congress what they want us to do. On the other hand, we shouldn't shy away from making a strong statement."

"The international group has a working definition," Board member Curtis Harper said. "If this body feels it can come up with something clearly better, fine. But I don't feel we need to come up with something just to be different. I would be in favor of using the IARC classification, at least for the moment."

Dorothy Canter, assistant NTP director, pointed out that the statement in the technical report applies only to the results of that particular test, while the IARC statement is based on all evidence available. "If the statements you make are to based only on one test, that's one thing; if on all evidence, that is something else."

"That's a good point," Nelson said. "We need to determine at what point we should expand to include all evidence."

"That is clearly our goal," Rall said. "The reports should be expanded to be more like monographs, and include all evidence available."

Nelson suggested a group should be established to study the question. "There is no need to make a decision now."

Rall and the Board worked out an agreement on a chemical nomination and selection process, after Board members complained about being bypassed.

The Board Subcommittee on Chemical Nomination and Selection had drawn up a plan in which chemicals would be nominated by NTP research and regulatory agencies, other government agencies, academia, industry, labor and the public. Nominations would be reviewed by NTP staff and then go to a chemical evaluation committee made up of representatives of NTP member agencies and the federal regulatory bodies. A final review would be made by a public advisory group, and the NTP Executive Committee (the heads of the member agencies) would make the final selections.

Rall and his staff modified that proposal to include an initial screening by a small NTP group. "This would involve a quick and dirty look at the nominations," Rall said, weeding out those which had already been tested, were on test or scheduled for test, or had been previously considered and rejected. No literature searches would be made, and staff could also make recommendations for additional types of testing not proposed by the nominating source.

That change did not bother Board members, but Rall's proposal to send nominations to the NTP Executive Committee without formally involving the Board or another outside peer review group drew their fire. The staff proposal would solicit "public advice" while internal review and executive committee consideration were in progress.

"The problem is that the chances of getting a separate public advisory group chartered are small. I decided that was not a viable proposal," Rall said.

"Couldn't a subcommittee of this Board do the job?" Horning asked. Rall replied that it could.

"I'll be frank," Nelson said. "I don't see much point in offering advice after the fact."

Rall responded that Executive Committee decisions would not be implemented immediately but would consist of approval of a prioritized list. "If you disagree later, that can be factored in."

"To be effective, then it seems to be this should be a thoughtful, deliberate process based on careful consideration. Delibrations of this Board should be one of the considerations of the Executive Committee," Nelson said.

"It is important that we not do it in a way that prolongs the process," Horning said.

"That's what you are urging," Rall answered. "These meetings are set up six months in advance. Theoretically and ideally, that's the right way to do it."

"Let's do it the right way," Nelson said. "The earlier recommendations of the Board and subcommittee stand. The Board seems willing to pitch in (and attend additional meetings). Basically, an orderly review process would include preparation of dossiers, assignment of them to Board members and outside consultants when needed, followed by meetings for discussion."

"You're talking about compounds for long term testing," Rall said. "How about those to be tested for mutagens?"

NTP plans to put about 500 chemicals a year on short term tests, and the Board agreed it did not need to be involved in making those selections.

In the selection process agreed upon, after the quick review by NTP staff, the chemical review staff at the National Center for Toxicological Research would perform literature searches and retrieve pertinent references. The staff would assess relevant data and prepare executive summaries of the information and propose testing needs.

The chemical review staff would then refer the nominated chemicals to the Chemical Evaluation Committee. Where necessary, subgroups would be set up to review chemicals for specialized types of testing. For example, a subgroup would be convened to evaluate the hundreds of compounds nominated annually for mutagenicity testing. The committee and any subgroups formed would be comprised of representatives from the Executive Committee member agencies with the needed expertise and experience. Primary and secondary reviewers would be assigned to each chemical referred to the committee or its subgroup to insure a thorough analysis of the data when recommendations are formulated. The chairman of

the committee would be responsible for making such assignments and would consider the nature of exposure, etc., in selecting reviewers so that appropriate regulatory concerns would be addressed.

Following evaluation by the committee, the chemical review staff would incorporate the recommendations in the executive summaries of the nominated chemicals and then prepare a list of chemicals recommended for testing, including the types of testing suggested which would be forwarded to the NTP core staff.

Staff would prepare a *Federal Register* notice on these chemicals soliciting data and advice from outside parties within a given time period (30-60 days). In addition, letters requesting information on the list of chemicals within the same time period would be mailed to interested groups and individuals. Data received as a result of this outside review process would be forwarded to the chemical review staff for assessment and incorporation in the executive summaries as necessary. NTP core staff would respond where advisable to comments and replies received as a result of the outside review process.

This information then would be presented to the Board subcommittee, and its recommendations would go to the Executive Committee.

Rall pointed out that a long term test of a single compound now costs about $500,000, justification enough for a careful and deliberate selection process.

ACCC CALLS FOR EXPANDED EFFORTS TO SUPPORT CHOP, OTHER PROGRAMS

The Assn. of Community Cancer Centers approved a resolution at its recent Second National Leadership Conference/Delegates Assembly in Denver directing ACCC officers to "apprise Congress and other key national leaders of the merits of the Community Hospital Oncology Program and other community cancer programs."

ACCC has been effective in building congressional support for community programs. Members indicated a desire to continue and expand that effort.

ACCC is particularly interested in CHOP, which will involve NCI contract supported efforts in 23 communities. The association is determined that NCI do the best evaluation possible of the programs. If the model works, ACCC intends to go back to Congress for money to help support development of similar programs wherever needed and appropriate.

The conference also approved a resolution to actively support a bill to provide terminal cancer patients with equity through early allowance of disability insurance.

Another resolution was approved formally defining a community cancer center as "an institution or program committed through organized activities to improving cancer care and cancer control." Basic components of community cancer centers were further defined:

1. Multidisciplinary cancer committees responsible for a cancer data system; cancer conferences; consultative, diagnostic and treatment services in surgery, radiation and medical oncology; and a system of quality of care evaluation.

2. Additional components include, but are not limited to, an oncology inpatient unit; oncology outpatient clinic; patient management guidelines; rehabilitation; psychosocial support; psychospiritual support; hospice, either hospital based or elsewhere; research; pain clinic; family support; detection clinic and screening; patient, public and professional education; and oncology nursing programs.

ACCC's seventh annual meeting, with the theme, "Community Cancer Care in the 1980s: Problems and Promises," is scheduled for March 6-8, 1981, at the Regency Hyatt Hotel in Washington.

DCT BOARD OKs RECOMPETING CONTRACTS IN NUTRITION, PLANT AGENT ISOLATION

Remaining concept approvals voted by the Board of Scientific Counselors of NCI's Div. of Cancer Treatment appear below. Other approvals of new programs and existing contracts scheduled for recompetition were reported in ***The Cancer Letter*** Oct. 10, 24 and 31. Those following are recompetitions, plus contract supported projects which will be renewed on a sole source basis.

Assessment of nutritional status of cancer patients. Estimated first year award $440,000 on three year contracts. The DCT staff narrative:

Present contractors are Brookhaven, Duke Univ., Emory Univ., Massachusetts General Hospital, and Texas Instruments. This project area was developed by the Diet, Nutrition & Cancer Program. In January 1980, these contracts were transferred to DCT based on their subject area and our expertise for scientific monitoring. The scientific basis for these contracts is that nutritional depletion is an important determinant of morbidity and mortality in cancer patients. Their focus is on evaluation of techniques for assessing nutritional status and using these techniques to investigate the pathophysiology of nutritional depletion in cancer patients. This group of contractors has evaluated the validity and accuracy of a spectrum of techniques for assessing nutritional status and body composition. These studies support the validity of standard anthropometrics in assessing body fat and the value of CT scan, total body water and body K and N by neutron activation in measuring the muscle compartment. These studies have also documented in humans the predominance of loss of muscle in the weight loss of cancer patients. Studies currently in progress are evaluating the effect of nutritional repletion on body composition, specifically looking at reconstitution of the muscle compartment.

We would plan to continue research in this subject but with some change in scope and emphasis. Within the limits of available technology, we would like each participating contractor to use common nutritional assessment tools including CT scan and total body potassium and total body water. We propose a change in emphasis from descriptive observation of weight loss in various compartments to intervention. We plan to systematically investigate the effect of different nutritional intervention strategies (such as varying the caloric source or the

amount of nitrogen) on changes in body composition. These contracts may allow us to develop particular methods of nutritional supplementations for specific patterns of nutritional depletion. Thus it may be possible to arrive at nutritional repletion protocols "tailored" to the specific form of weight loss patients experience.

Services in support of the drug screening program. Estimated first year award, $300,000 on a three year contract. The narrative:

IIT Research Institute is the present contractor. The major tasks of this contract are:

1. Evaluation of the prescreen test data for all new synthetic materials and natural products; requesting further testing as required, notifying both suppliers and staff of those demonstrate activity; scheduling them for review by the Prescreen and Data Review Subcommittee meetings and participation in these meetings.

2. Initiate requests for testing to screening contractors for those compounds designated for evaluation in the panel of in vivo test systems; assist in the evaluation of these test results, and maintain an automated file of the evaluations and status of these compounds.

3. Provide the capability to evaluate potential use of ADP for more efficient implementation of the tasks of this contract. They have automated a file for recording requests for additional compounds required for testing. They have provided the analysis and programming necessary for establishing a file for compounds of interest to staff and the Operating Committee file. They coordinate the data input for these files which include the minutes of the Operating Committee meetings, as well as the input from staff of the Div. of Cancer Treatment on the status of all compounds being followed by the Operating Committee. This data includes such items as procurement requirements, screening test results, toxicology status, and Decision Network status. These files were designed to provide a management tool for DEB staff and can be queried to provide reports for staff on individual compounds or by subject, such as Operating Committee minutes.

It is anticipated that new test systems, such as the human stem cell cloning assay, will be added to panel of test systems. This contract will continue to provide the personnel to assist in the evaluation of these more sophisticated test systems, as well as assistance in analysis for the upgrading of the automated files and systems for easy access to the status of compounds of interest. It is planned that the contractor will provide the expertise and assistance to DEB staff in developing automated graphics capability, automation of additional files to enable easy and accurate retrieval of necessary data, and assistance in developing better on-line communications with DCRT computers.

Isolation of antineoplastic agents from plants. Estimated first year award, $450,000 on three year contracts. The narrative:

Present contractors are Arizona State Univ., Purdue Univ., and Univ. of Illinois. The function of these contracts is to isolate and characterize compounds responsible for the antitumor activity of plants assigned by the project officer. The work involves preparation of extracts, solvent partitions and extensive chromatographic separations to isolate the active components of assigned plants. These isolations are guided at all stages by bioassays either done in house or by NCI screening contractors. Approximately 20 to 30 plants are under investigation by each contractor at any given time and active materials are isolated and characterized from several plants per year per contractor. Isolation and identification of the active components of a plant typically takes one to three years due to the extreme chemical complexity of the starting plant extracts and the necessity to bioassay at each stage of the isolation procedures. Characterization of the isolated compounds is performed by evaluation of spectroscopic data, inter-relation with known compounds and x-ray crystallography.

In order to obtain sufficient pure compound for in vivo testing plants are worked up in lots of 50-200 pounds depending on the relative amount of extract obtained from the plant. Each isolation step is initially conducted on a small scale and the fractions are bioassayed to determine whether the activity is retained and whether the separation is useful in concentrating activity. This is followed up by processing the material on a large scale.

In addition to isolation and characterization of new materials, the contractors are also responsible for re-supplying active compounds for tumor panel testing and for reisolation of activ active plant derived compounds from other suppliers when the original suppliers are unable to provide NCI with sufficient material for testing.

During the first 18 months of the current contract the three contractors have isolated 22 pure compounds with in vivo or in vitro activity from 12 different plants. With the exception of the five most recent isolates all of the compounds have been completely or nearly completely identified. Further antitumor screening is under way on all compounds showing in vivo activity. One compound, phyllanthostatin, has shown good activity in the B16 melanoma and is likely to be a Decision Network 2A candidate. Scaleup isolation of 12 compounds for tumor panel studies which were isolated under earlier contracts has been completed. A total of 66 plants is being actively fractionated and 12 of these appear promising enough to be potential sources of future DN candidates if the activity holds up and if the isolated compounds are of novel structural types.

Work will be continued on plants of useful interest to NCI and active compounds will continue to be isolated and characterized. As new good leads are found through the NCI plant screening program plants will be recollected in several hundred pound quantities and assigned to the chemists for isolation studies to replace plants completed. No major changes are contemplated in the basic workscope of these contracts. The addition of new in vitro prescreens to the screening program should increase the number of new leads available.

The Board approved a new contract supported project in the Developmental Therapeutics Program for computer substructure searches, at an estimated $42,000 for three years, which will be competed through small business set aside. Competition will be limited to a list of firms deemed qualified by the Small Business Administration.

The Board also approved three noncompetitive renewals of existing programs:

—Adjuvant chemotherapy trials in head and neck squamous carcinoma for a total of about $1 million a year, with Univ. of Cincinnati, Univ. of South Florida, Univ. of Texas, Univ. of Maryland, Memorial Hospital, Univ. of Michigan, Northern California Oncology Group, and Radiation Therapy Oncology Group.

—Enzyme prescreen development and a study of potential antitumor agents from marine and other unique sources, with Microbial Chemistry Research Foundation, for an estimated $175,000 a year.

—NCI-PAHO collaborative cancer treatment research program. with the Pan American Health Organization, for an estimated $200,000 a year.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the Contracting Officer or Contract Specialist named, Research Contracts Branch, National Cancer Institute, Blair Building, 8300 Colesville Rd., Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CO-14343-38

Title: *Cancer Information Dissemination and Analysis Centers (CIDACs) covering carcinogenesis and/or cancer virology, immunology and biology*

Deadline: *Jan. 7*

NCI intends to issue an RFP to obtain the services of one or two organizations with demonstrated scientific and technical capabilities to assume the operation of two Cancer Information Dissemination and Analysis Centers for the International Cancer Research Data Bank Program. One contract will be awarded for each of the two CIDAC subject areas: 1) carcinogenesis; and 2) cancer virology, immunology and biology. Offerors may submit proposals in more than one area and be considered for award of more than one CIDAC contract.

In these two subject areas, the CIDACs serve as the major resources for providing to the ICRDB Program scientific guidance essential for maintaining the high quality of ICRDB publications and services designed for cancer researchers. The major activities of a CIDAC include:

1. Assuming regular production of 20-25 different "Cancergrams" (monthly current awareness bulletins containing 30-100 abstracts of recently published cancer research). For each Cancergram topic, a CIDAC staff member regularly screens, sorts, and categorizes abstracts retrieved from computerized searching of an ICRDB data base. The resulting package of abstracts is then reviewed by a consultant (identified by the CIDAC) who is currently involved in research pertinent to the Cancergram topic area, and who need not be an employee of the organization. In order to meet short production deadlines, it is essential that the work of the subject specialist and the consultant-researcher for each monthly Cancergram can be completed with a turnaround time of a few days.

2. Producing annually 10 different "Oncology Overviews" (retrospective compilations of 100-500 selected abstracts on high interest cancer research topics). These publications are developed by the subject specialists in consultatation with researchers (identified by the CIDAC) who are recognized as experts in the subject area of each Oncology Overview.

3. Responding rapidly to requests for information in specific cancer research subject areas.

4. Planning and implementing innovative projects to promote communication and exchange of technical information between cancer researchers. The organization must have previous experience in analysis and processing of cancer research information or similar biomedical information. The project director must have a PhD or MD in a biomedical subject relevant to research, and administrative experience. Subject specialists must all have at least an MS or equivalent (approximately half should have a PhD or equivalent), plus research experience in a biomedical subject area relevant to the CIDAC subject area, and collectively they must be able to cover all subject areas relevant to the CIDAC. The consultants for Cancergrams must all have a PhD or MD and current research involvement in biomedical subject areas directly relevant to the Cancergram each will be reviewing. Collectively they must cover all Cancergram topics within the CIDAC's purview, and should be located within approximately a 25-mile radius of the CIDAC office.

Contract Specialist: Barbara Mercer
Biology & Diagnosis
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NCI CONTRACT AWARDS

Title: Operation and enhancement of NCI's chemical information system, supplemental agreement
Contractor: Chemical Abstracts Services, $80,000.

Title: Studies on preclinical canine bone marrow transplantation, continuation
Contractor: Hazleton Laboratories, $145,000.

Title: Literature monitoring service
Contractor: Enviro Control Inc., $292,102.

Title: Qualitative and quantitative analysis of proteinaceous substances
Contractor: Univ. of Iowa, $318,124.

Title: Operation of a primary genetic center for rodents in biocontainment environments, 10-month extension
Contractor: Harlan Industries, Indianapolis, $299,980.

The Cancer Letter _Editor Jerry D. Boyd

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