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THE CANCER LETTER

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"Don't Judge Me On A Snapshot In Time," Broder Says In Responding To Criticims By Cancer Centers

It is "premature" for the cancer centers community "to pass judgment on my response to problems facing the centers," NCI Director Samuel Broder said in answering criticism aimed at NCI leadership by members of the Assn. of American Cancer Institutes (**The Cancer Letter**, June 30). "I'm

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In Brief

Arlan Gottlieb, CALGB Leader, Dead At 55; NCI's John Cooper Undergoes Heart Transplant

JOHN COOPER, chief of the Extramural Programs Branch in NCI's Div. of Cancer Etiology, underwent a heart transplant June 14 at the Texas Heart Institute of St. Luke's Episcopal Hospital in Houston. He is living in an apartment in Houston while convelescing, and told **The Cancer Letter** last week that tests show his immune status is satisfactory with no signs of rejection. He plans to retire from the government when his sick leave and annual leave expire next year, and will live in a home he and his wife purchased in San Marcos, TX. Genrose **Copley** has been named acting chief of the branch. . . . **ARLAN GOTTLIEB**, professor of medicine and chief of hematology at SUNY Health Science Center (Syracuse), died June 12 after a year long illness. He was 55. He was chairman of the Lymphoma Committee of Cancer & Leukemia Group B, a member of NCI's Clinical Cancer Investigation Review Committee and former CCIRC chairman . . . . **BIPARTISAN TASK** force on tobacco and health has been established by 35 members of the House of Representatives. The group is headed by Richard Durbin (D-IL) and Bob Whittaker (R-KS). Other members include key health legislators Henry Waxman (D-CA), chairman of the House Health Subcommittee; and Fortney Stark (D-CA), chairman of the House Ways & Means Health Subcommittee. The task force will attempt to educate members of Congress and the public on tobacco use and its health effects; build coalitions with other congressional and public groups interested in tobacco related issues; develop strategies for advancing tobacco related health legislation; and assist members of Congress in addressing problems associated with tobacco use. . . . **ROBERT STRUCK**, who heads Southern Research Institute's Biological Chemistry Div., has received SRI's Scientific and Engineering Excellence Award for his research in development of new compounds and approaches for treatment of cancer.

Broder: "Give Sam Broder A Chance; I Will Listen; I'll Return Calls"

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an unknown to most centers people. They need a chance to get to know me. I hope they don't judge me on a snapshot in time."

Center directors and staff members were highly critical of NCI for what they felt was lack of concern about problems in the Cancer Centers Program: the flat budget, which has resulted in cutting the number of funded center core grants by four this year, and will reduce it further next year unless more money is added; the chronic underfunding of grants at less than recommended levels; staff reductions in the program, with the slots apparently moved to other programs; and the foot dragging on relocating the program.

"The cancer centers community should have more patience with the new director," Broder told **The Cancer Letter**. "Many of the problems antedated my appointment. They should judge me on the basis of what happens from now on. I have gone out of my way to stress to Congress the damage that could occur. Cancer centers are a major foundation of the National Cancer Program.

"I hope the centers people will allow me the time to do the job. Sam Broder has not had the opportunity to respond to these problems. Give Sam Broder a chance."

Broder said that NCI has taken steps to comply with the recommendations of the Institute of Medicine's report on cancer centers. "We have launched development of a five year plan, working out of my office." Deputy Director Maryann Roper heads the NCI committee which has been assigned that task.

Broder noted that new requirements for recognition of cancer centers as "comprehensive" have been agreed upon in general by the National Cancer Advisory Board and NCI and that staff work on the new guidelines should be completed this summer.

"I take the comprehensive centers very seriously," Broder said. "I can't imagine a better engine to drive every element of the National Cancer Program than comprehensive cancer centers. I hope the new guidelines can be in place by the end of the year." Approval of the NCAB will be required.

As for AACI members' complaint that their efforts to sell Congress on accepting recommendations on funding made in the IOM report were undercut by the NCAB's lukewarm reception of it, Broder pointed out that NCAB members "don't work for me. They are appointed by the President. Several said at the board meeting that they would register objections to it [primarily to the suggestion that funds should be reprogrammed from other areas to beef up the core grant budget]. But it's not fair to say that we are not paying attention to it."

However, Broder added, "Adherence to the IOM report is not a litmus test of our commitment to the centers program."

Centers representatives were disturbed when the Div. of Cancer Prevention & Control asked its Board of Scientific Counselors to approve a concept for minority cancer centers demonstration program and fund it out of the centers core grant budget. That would have started with the 1990 budget, when it appears that five or six more core grants will be lost unless more money is added. The board tabled the concept, indicating that either more money should be added to the centers program for that purpose or it should be funded from the cancer control line item appropriation.

"I would be deeply disturbed if programs for minorities and the elderly would be seen by the centers community as something in competition with centers," Broder said. "Centers should be leading a national effort in those areas. They will gain in moral authority if they do. I'm obsessively interested in reducing cancer death rates. I don't think any of us can be satisfied with it now, and especially with the differentials. We have to do more. We can take satisfaction in what we have done, but we need to do more.

"Perhaps, absent compelling evidence to the contrary, the first assumption that should be made is that I know what I am doing. I will listen to any suggestions they care to make. I'll return phone calls."

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Broder met with several cancer center directors during the society meetings in San Francisco. Apparently, there was a frank exchange of views, but with little movement toward a consensus.

Richard Steckel, director of the UCLA Jonsson Comprehensive Cancer Center, summarized his view of the exchange in a letter to Broder, copies of which were circulated at the AACI meeting [Steckel was unable to attend the meeting in Puerto Rico because of an ailing back]. Excerpts follow:

"You started our meeting with what seemed to me an apology for being 'blunt' with us. Certainly no apology is needed for stating your views forthrightly, which you did. I hope you also understand better now the commitment of center directors to the NCI centers program, because we have experienced first hand how core grants have encouraged 'centerness' along with the development of quality interdisciplinary research at our institutions.

"In serving as sincere advocates of the Cancer Centers Program, we have sometimes been blunt also. However, we emphasized to you that cancer center directors have also been highly supportive of the National Cancer Program as a whole, particularly with respect to the congressional appropriations and authorization processes. Center directors have not simply 'looked out' for the centers program. It also won't surprise you that there is no single philosophy (concerning the roles of centers and their priority relative to other NCI programs) which is shared by all center directors. When you encounter opposition to certain NCI initiatives by individuals from centers who are on the DCPC Board of Scientific Counselors, as you did recently, you are not necessarily receiving the views 'of center directors.'

"In fact, most of us are deeply involved in providing care for minorities and for other underserved individuals, including the elderly, in our geographic regions. Furthermore, much of our cancer control and prevention research at centers and some of our treatment research are focused on individuals from underserved populations, and perhaps this important point has not yet been adequately conveyed to Congress. When you said that centers should 'invest' more now in addressing the problems of underserved populations as part of our research and service activities, we noted to you that we will be enthusiastic about doing this if we are involved directly by the NCI leadership in developing new strategies and initiatives for centers and if our ongoing activities and successes in these areas are conveyed to Congress. . . While we are quite willing to do this in concert with you, we need to feel that you appreciate what we are doing already and that we can have an impact on the development of NCI policies and strategies as centers.

"We would also like to be confident that the NCI leadership and Congress fully understand the significance of core grant support for centers in relation to RO1 and PO1 supported research. Much of what constitutes center core grants (e.g. research core services, salaries, developmental funds, etc.) directly offsets certain costs that would otherwise have to be borne directly by RO1 and PO1 supported projects. Furthermore, core grants may still be the best 'investment' NCI can make to extend its reach (with a relatively limited number of dollars) into populous regions and academic institutions around the country: the core grants serve as magnets to draw in substantial institutional and private community support for cancer research, which in the long run will exceed the core grants by a considerable amount.

"You also stated . . . that you were distressed with the oppositional views of center directors about splitting off basic science centers from the centers program [because basic science centers are getting an increasingly larger share of the core grant budget in peer review]. . . Center directors are not simply 'looking for security in numbers' rather than addressing scientific needs, as you first implied . . . A modification of the review mechanism for cancer centers might be worth considering now, or at least an attempt to normalize core grant priority scores for basic science centers against other basic science centers, for comprehensive centers against other comprehensive centers, clinical centers, etc., rather than to compare core grant priorities in ways that suggest all centers are from the same mold. . .

"It really doesn't seem reasonable to regard priorities for core grants as being identical with peer review priorities for research projects. While all centers should be expected to rise or fall eventually on the basis of peer review, there are completely different criteria applied to the reviews of core grants than to research project grants, and the apparent similarity of priority scores between centers and PO1 and RO1 grants is illusory. Centers are supposed to be judged individually by peer

by peer reviewers for their success in promoting interdisciplinary cancer research and for creating interactive research programs 'in which the whole is greater than the sum of its parts.' Core grant reviews introduce additional criteria for the assignment of priority scores which have nothing at all in common with RO1 or PO1 grant reviews. Therefore, normalization of the priority scores for different types of centers again may be indicated, whether or not all of the centers are funded from a single budgetary pool.

"Finally, if there is a point of unanimity among center directors it is that a continuing and substantive dialogue should be conducted between the centers and NCI leadership, along the lines of our extended discussion in San Francisco. If center directors are expected to 'buy into' initiatives which are proposed by NCI and if centers are to make their maximum contributions to the National Cancer Program, a regular dialogue of this type is a necessity.

"Whatever administrative changes are undertaken with respect to the organizational position of the centers program at NCI, we hope the importance of this point will be recognized. Obviously, strong intramural staffing of the centers program with access of its leadership to an appropriate level of NCI decision making will be equally important."

On that last point, the displeasure of AACI members over the NCAB and NCI leadership reactions to the IOM report has hardened their position on relocating the centers program. AACI has gone on record asking that the Cancer Centers Program be moved from the Div. of Cancer Prevention & Control into a new division. Failing that, they want it moved into Broder's office.

The issue of funding the minority demonstration centers out of the core grant budget, and the deplorable situation with loss of staff positions, has convinced centers people that they will never get a fair shake in DCPC.

Robert Capizzi, director of the Cancer Center of Wake Forest Univ., commented on the minority issue in a letter to Ross McIntyre, immediate past president of AACI.

If the DCPC proposal on minority demonstration centers had gone through, "programs related to basic science and clinical investigation would obviously be underwriting the cost of the cancer control projects," Capizzi wrote. "I think this is another case in point for further pressure on NCI to relocate the Cancer Centers Program. Its incorporation administratively in the cancer control division continues to place the centers program in a second run position. I have no disagreement with Peter Greenwald's agenda for cancer control. However, I do disagree with his methods of financing it."

Ray Morrison's letter to AACI after he retired from the centers program staff (**The Cancer Letter**, June 30), added this to the arguments for moving the program out of DCPC:

Lamenting the drastically reduced centers program staff, down to one program director, Morrison noted there had been six, with three secretaries. "Even that was supplemented by a substantial support contract which in effect provided for additional personnel. It is my interpretation that these slots have all been absorbed into the cancer control activities of DCPC since the staffing for those purposes has dramatically increased in recent years."

Organ Systems Move, Other Changes, Corrections Noted In NCI Directory

As predicted, the ink was barely dry on **The Cancer Letter**'s directory of frequently called numbers at NCI when changes were made (and a few typos turned up). It is suggested that readers note these changes in the directory as follows:

Page B10--Move the Organ Systems Section from the DCPC Cancer Centers Branch to the DCBD Extramural Research Program on page B6, and elevate it to a branch. For the moment, the room and phone numbers remain the same.

Page B9--John Cooper, chief of the Extramural Programs Branch in DCE, is on medical leave (see *In Brief*) and is planning to retire. Dr. Genrose Copley is acting chief.

Page B6, DCE--Jean Mcammon is acting administrative officer at FCRF; drop Karen Faunce as one of the AOs for the Biological Carcinogenesis Program; Takis Papas' room number as chief of the Laboratory of Molecular Oncology is Bldg 469 Rm 169.

Page B7--Stephen O'Brien's address as chief of the Genetics Section in the Laboratory of Viral Carcinogenesis is 560/11-85, and the phone is 698-1299; drop the Viral Leukemia & Lymphoma Section; Harry Gelboin's address as chief of the Metabolic Control Section in the Laboratory of Molecular Carcinogenesis is Bldg 37 Rm 3D28, the phone is 496-6365; Michael Sporn's address as chief of the Laboratory of Chemoprevention is Bldg 41 Rm C629.

Page B8--Snorri Thorgeirsson's room number as acting chief of the Biopolymer Chemistry Section in the Laboratory of Experimental Carcinogenesis is Bldg 37 Rm 3C09.

Page B9--Robert Hoover is acting chief of the Population Studies Section in the Evironmental Epidemiology Branch; his address and phone is the same as his listing as chief of the branch.

Page B10--Scratch the phone numbers listed for Edward Sondik as acting associate director for the Cancer Control Science Program and acting chief of the Cancer Control Applications Branch; he can be reached at his number as AD for the Surveillance Program, 496-8506.

Page B1--Mary Knipmeyer has left as NCI legislative liaison and a search is on for a successor. The office staff, at 496-5217, is taking legislative related calls.

Other changes will be published as they are called to our attention.

DCE Board Approves Recompetitions, PA On Cancer In Fish, Shellfish

Six contract concepts worth a total of nearly $12 million, including recompetition of five existing contracts, were approved last week by the Div. of Cancer Etiology Board of Scientific Counselors.

The largest of the contracts is a $3.39 million, five year project that is the major source of support to the DCE director's office. The contract is currently held by Technical Resources Inc.

The board also approved, after acrimonious discussion, a controversial program announcement soliciting applications for research on cancer in fish and shellfish. The program announcement proposed that a special study section be convened to review the applications, since previous applicants were generally unsuccessful in the regular review.

Also approved were two interagency agreements between NCI and the National Institute of Occupational Safety & Health. One agreement provides $60,000 for a feasibility assessment for a study of the herbicide alachlor. The second agreement provides $20,000 for a feasibility assessment for a study of workers exposed to ortho-phenylphenol, commonly used as fruit and vegetable fungicides.

The concept statements and discussion follow:

Resource to support the chemical, economic and biological information needs of the Div. of Cancer Etiology. Recompetition of contract held by Technical Resources Inc. Five years, $3.39 million. Estimated first year award $627,000.

This project is the major source of support to the office of the DCE director for the development of information in the areas of environmental and occupational cancer. The project was initiated over 13 years ago and has been recompeted three times since. The present contract began in August 1987 and consists of four major tasks.

Task 1 supports NCI's Chemical Selection Working Group in selecting and nominating chemicals to the National Toxicology Program for in carcinogenicity bioassay program. NCI has been a primary source for nomination of candidate chemicals to NTP. One of the primary functions of the contractor is to gather information and prepare summary sheets on candidate chemicals. Summary sheet preparation has averaged 74 professional hours, 73 semiprofessional hours and 45 support staff hours per summary sheet.

This program will continue at the present rate, which will require the preparation of 30 summary sheets per year, for a total of 150 summary sheets for the five year period. Should the NTP staff increase or decrease the number of chemicals they will be able to test for carcinogenicity, adjustments to the number of summary sheets may become necessary. Current plans are to conduct two class studies per contract year. Nominations to the DCE in vitro testing program are anticipated at the rate of 20 to 30 per year.

Task 2 provides support for the International Agency for Research on Cancer. DCE, through contractor assistance, provides the major collection of data and the preparation of first drafts of Section 1 and Section 2 of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Considerable effort is involved in the production of these drafts and answering questions developed during the actual monograph meetings. Contract support for a typical IARC working group meeting has averaged 335 professional hours, 954 semiprofessional hours and 548 support staff hours. DCE anticipates providing to IARC, for two or three working group meetings per year, a total of 10 to 15 meetings, the information required for the IARC Monographs. This will involve from 50 to 60 chemicals per year, or about 250 to 300 chemicals in total.

Task 3 deals with the development and maintenance of data for the Chemical Carcinogenesis Research Information System. This is an evaluated and fully referenced data base, containing carcinogenicity, mutagenicity, tumor promotion and tumor inhibitor test results. The mechanism currently in place for gathering information and data will be continued. DCE expects that these sources will provide approximately 250 to 300 new chemicals not previously entered into CCRIS for evaluation and classification.

Task 4 allows NCI to conduct special studies and prepare reports. For example, reports have been prepared on the evaluation of carcinogenicity and mutagenicity of organic and inorganic contaminants in drinking water, inhibitors of chemical carcinogenesis, and species to species comparison of carcinogen metabolism. This task also provides for review, editing and publication of those class studies. Bioassay Report Summaries are prepared of the NTP Technical Reports for inclusion in the Bioassay Report Summary Handbook.

The contractor also assists this division in responding to ad hoc inquiries, ensuring a quick turn around. Efforts in task 4 will be governed by budgetary considerations. With the proposed level of funding, they will be limited to the preparation of Bioassay Summary Reports at an anticipated rate of 20 to 25 per year, review, editing and publication of class studies conducted in support of the chemical selection process.

The concept was approved unanimously.

In vitro evaluation of chemical candidates for in vivo testing. Recompetition of a contract held by Microbiological Associates. Two awards, the mouse lymphoma assay and the salmonella assay, four years each, total $1.275 million. Mouse lymphoma assay total $1.02 million, proposed first year award $240,000. Salmonella assay total $255,000, proposed first year award $60,000.

Since May 1981, the office of the director has had in place

competitively awarded contracts to perform mutagenicity assays (Ames salmonella microsome plate assay and mouse lymphoma L5178Y TK+/-) for support of extramural and intramural activities of DCE. The primary thrust has been to support the NCI selection process for carcinogenicity testing in the National Toxicology Program. The division has evolved a format to look at large groupings of chemical to systematically select the best candidates. This has routinely shown that there is a paucity of in vitro data on most of the compounds. Data obtained from these in vitro contracts have been helpful in permitting the selection group to make more informed decisions in a timely fashion. It should also be noted that because the program concentrates on examining compounds or classes that have generally not been examined before, DCE frequently presents the contractor with difficult testing problems.

To continue this support to intramural and extramural activities, approval is requested to initiate a competitive renewal of two four year contracts, the salmonella microsome plate assay and the mouse lymphoma assay. Each contract will be expected to report on 20 to 30 compounds per year, which approximately one third of the compounds supplied requiring an additional assay before a final report on the compound is written. The expected cost per compound is $2,000 for the salmonella assay and $8,000 for the mouse lymphoma assay.

Each compound will be tested in up to five tester strains of salmonella typhimurium both with and without S9 metabolic activation. 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 controls will also be included in each assay.

Test compounds are normally procured through another contract, and aliquot portions will then be supplied to the laboratories conducting the assays.

Board member William Benedict asked whether the work on the two contracts is done simultaneously. Thomas Cameron, the project officer, explained that the contractor uses the same solvent for both assays. Board member Lawrence Fischer asked about disseminating information on the chemicals. Cameron said NCI publishes its intent to test specific chemicals, and results are published in the National Toxicology Program's "Annual Report on Carcinogens." DCE Director Richard Adamson noted that the report in entered into the Library of Medicine's database.

The concept was approved unanimously.

Procurement of polyclonal and monoclonal antibodies to papillomavirus proteins and to associated cellular proteins. New contract. Four years, total $1.29 million. Proposed first year award $300,000.

The objective of this contract is to obtain specific polyclonal rabbit antibodies and multiple mouse monoclonal antibodies to specific papillomavirus proteins and to the human and murine cellular proteins that have been found associated with the papillomavirus proteins, such as the retinoblastoma gene product p105, the human and murine p53, and the human and murine p107. These antibodies will be used in ongoing studies of the molecular mechanisms of papillomavirus transformation and to gain insight into the pathogenesis of papillomavirus infections.

The contractor will be provided with either peptide or protein preparations to be used as antigen. The contractor will also be provided with immunization schedules for both mice and rabbits. For the production of rabbit polyclonal antibodies, the rabbits will be injected intradermally and bled according to the protocol provided. The individual rabbit's serum from each bleed will be separated, labeled and frozen at -20 degrees C in sterile plastic liquid scintillation vials. The contractor will deliver to the principal investigator the frozen serum samples on a weekly basis. Approximately 15 to 20 different peptide specific rabbit antisera will be generated during the first year.

For monoclonal antibody production, the contractor will provide serum samples from immunized mice (10 animals per group, 25 to 100ul of serum from each animal) for evaluation by the principal investigator. The principal investigator will then instruct the contractor which mouse spleen should be used for fusion. The contractor will remove and fuse the designated spleens and screen the resulting hybridomas as instructed. Positive hybridomas will be single cell cloned by the contractor, rescreened for antibody production and expanded prior to delivery to the principal investigator. Approximately seven to eight different proteins will be generated during the first year.

A 4 percent cost of living increase is budgeted into each year subsequent to the proposed first year budget of $300,000.

Board members were enthusiastic about this contract concept. Janet Butel noted that the cost to individual investigators to produce these reagents is prohibitive. "There's clearly a need for additional reagents," she said.

Fischer asked about the possibility of setting up a laboratory within NCI to do this work. Adamson said that contraints on the number of full time employees would take slots away from other DCE activities.

The concept was approved unanimously.

Chemical carcinogen reference standard repository. Recompetition of a contract held by Midwest Research Institute. Five years, total $2.25 million. Proposed first year award $415,000.

The Chemical & Physical Carcinogenesis Branch has maintained a Chemical Carcinogen Reference Standard Repository under contract since 1974. The repository has provided authentic, documented reference standards of polycyclic aromatic hydrocarbons, metabolites, nitrosamines, aromatic amines, food mutagens and many other chemical classes to researchers as an essential aid to their investigations.

The objective of this concept is to recompete the current contract for the operation of the chemical repository. The contractor will provide safe storage for milligram to kilogram quantities of many types of chemical carcinogens, mutagens, anticarcinogens and related chemicals. The contractor will dispense these compounds upon request by the NCI project officer to the scientific community.

The contractor will maintain the CCRSR and provide a centralized source of well characterized and documented reference compounds for the carcinogenesis research community. Safe storage will be provided for stock quantities of chemical carcinogens, anticarcinogens and related chemicals. Upon authorization by the NCI project officer, samples will be prepared, packaged and shipped to designated requestors all over the world. Analytical characterization data will be provided, as well as information on safe handling of each chemical. Repository stocks will be received from four CPCB synthesis contractors and from surplus, reanalyzed stocks of the National Toxicology Program. Some chemicals will be obtained commercially and analyzed for purity as needed to support the in vitro screening program of the DCE director's office.

A "payback" system has been initiated, applying a charge to requestors for chemicals shipped to individual laboratories. This charge helps to partially offset the cost for producing the chemical reference standards which are supplied to the repository by the four individual synthesis contractors. Beginning with the effective date of the current contract, from September 1985 to Feb. 1, 1989, the repository has shipped a total of 1,704 chemical compounds and received payment of $292,937. These funds received by the contractor are deducted from the amount billed to NCI for contract services. Payback will be a feature of the new award as well.

The repository maintains a computerized inventory system which provides a monthly status report on shipping and receiving activity. In addition, the inventory system provides storage of data on chemical and physical properties and available information of safety and disposal. Property data sheets, which accompany chemical shipments, are generated from the inventory system. Also, fiscal information is computerized for billings and payments for chemicals shipped.

This resource program seeks, not only to assure a supply of reliable research material, but also to assure the safe handling of these dangerous materials at all steps in their processing, from receipt at the repository to receipt by the user of a

package that can be opened in complete confidence.

The repository contractor is nearing completion of a "Handbook of Analytical Data" on polycyclic aromatic hydrocarbon metabolites. The first volume will cover about 60 metabolites of benzo-a-pyrene. Future volumes will consist of similar information on metabolites other than PAH. There is no other compiled source of documentation on the PAH metabolites available commercially and we expect to make these volumes available to the research community under the payback provision of the repository.

David Longfellow, chief of the Chemical & Physical Carcinogenesis Branch, said that as of June 1, the payback system in the contract had generated $356,000, or 20 to 25 percent of the contract. Board member Anna Barker asked whether the payback is sufficient.

"We're pushing the limit of what the market will bear," Longfellow said. He said the purpose of charging for the compounds is to make recipients aware of their actual cost. Adamson said that the cost should not be so high that the extramural community will not use the repository. "And we can't make money on it," he quipped.

The concept was approved unanimously.

Studies on the etiology of neoplasia in poikilothermic, aquatic animals: finfish and shellfish. Program announcement. (No funds are specifically set aside for applications responding to a program announcement, but are funded out of money established during the NCI budget development process for grant funding.)

It has become evident that "cancer epidemics," or epizootics can occur in certain fish populations. At present, there are at least six areas within the U.S. that appear to present significant epidemics: Puget Sound Basin in Washington, Torch Lake in Michigan, the Black River in Ohio, the Buffalo River, Hudson River and Pamlico River in Texas. In each case the feral finfish population presents an unusually high prevalence of distinct tumor types.

Experimental evidence suggests that some fish species when compared to rodents are less sensitive to the toxic and more responsive to the carcinogenic effects of xenobiotics; they react more promptly, with a shorter latency period and with greater specificity. These characteristics suggest that they should serve as major indicators of agents in the environment which may pose a risk to humans. Not only are these animals candidates to serve as sentinels of carcinogenic pollutants in the environment, but the epizootics of cancer which they experience in confined water areas such as lakes and canals, or confined areas of bays, offer a natural experiment for establishing cause and effect relationships, interspecies comparisons and for establishing target cells at risk.

An RFA for "Studies on the Etiology of Neoplasia in Poikilothermic, Aquatic Animals" was issued in January 1986. The purpose of the RFA was to develop a broad spectrum of studies that would facilitate the understanding of the etiology of neoplasia in finfish and shellfish. Fifty-four applications were received in response to the RFA and a total of nine awards were made. The RFA was jointly sponsored by NCI, the National Institute of Environmental Health Sciences and the Department of the Army.

A number of the unsuccessful applicants have revised and resubmitted applications which have been assigned to the usual Div. of Research Grant study sections. These and other applications on the etiology of cancer in fish have uniformly fared very poorly (one in 24 funded in three years). The study section reviewers generally have considerable personal experience with warm blooded animals, particularly rodents and have little or no appreciation for feral fish as environmental sentinels or as laboratory models for carcinogenesis.

The overall purpose of this program announcement is to accelerate the development of additional understanding relative to studies on the possible etiology of neoplasia in poikilothermic, aquatic animals. The proposed PA will seek again to make the research community aware of the interests of NCI and its other collaborating agencies in fish carcinogenesis models. The announcement will seek applications for an Oct. 15, 1989 deadline. An unusual feature of this initiative provides that all responsive applications will, in turn, be reviewed by a special study section to be assembled by the Div. of Extramural Activities. The study section membership will have the requisite expertise and experience with aquatic animal models to offer a true peer scientific merit review. Secondly, the seven grants which were awarded in response to the first RFA for four years, will be given the opportunity to respond to the deadline for competitive renewal. We believe that the special review group and the PA to announce NCI's continued interest are appropriate in view of the poor track record of this developing area in the standard DRG review.

Listed below are some commonly identified needs which are intended to express the spectrum of studies of interest but which are not intended as a comprehensive list:

--Evaluation of the similarity of metabolic function in procarcinogen activation among different species of invertebrates.

--Effects of environmental and physiological variable of water temperature, age, sex and gonadal development bioavailability and metabolism of xenobiotics.

--Development of in vitro culture systems for normal and neoplastic cells from invertebrates and vertebrates and analysis of adducts to macromolecules of environmentally relevant xenobiotic metabolites.

--Studies on chemical and chemical/viral interactions in the etiology of aquatic animal neoplasms and the identification of oncogenes.

--Analysis of DNA repair capacity, mitotic index, sister chromatid exchange, cell cycle time and enzyme pathways for xenobiotic metabolism under various temperature conditions in poikilothermic aquatic animals and determination of the relationship to the persistence of genetic lesions that might lead to tumorigenesis.

--Studies of factors involved in promotion or progression of a tumor in aquatic species. Assessment of transplantability of neoplasms.

--The effect of chemical pollutants on the immune response in aquatic animals and the role of the immune system in aquatic animal neoplasia.

--Expansion of the experimental oncology database on various promising fish species as carcinogen assay subjects. Studies might include the development of data on potency of carcinogenic agents in fishes.

Fischer asked for clarification of what the board would be voting for on the program announcement. Longfellow explained that the vote basically is whether there should be a special study section for applications for the originally RFA.

"The overall goal is to attract investigators in carcinogenesis to work with those who have experience in working with fish," he said.

Board Chairman Hilary Koprowski asked why this work should be done by NCI, rather than the Dept. of the Interior. Longfellow said other groups had been brought in to work on an atlas of cancer in fish.

Board member Thomas London noted that the thrust of the study seemed to be the mechanism of cancer in fish. "I would think our board would be more interested in the transmission of tumors to humans," he said. Longfellow said such studies would be included.

Koprowski said that 30 years ago, "we learned an enormous amount studying human tumors in rats. I don't see much worth in going through the same thing in fish. I wonder if this is the organization to support this. I suspect that's the reaction you're seeing in the regular study section."

"We're not interested in curing cancer in fish," Longfellow responded. Since fish develop tumors quickly, the study of trophic transfer and oncogenes in fish could be less expensive than using other animals. The fish can also serve as environmental "sentinels."

Fischer suggesting adding one or two aquatic experts to the existing study section. Barker asked, "Is the intent to establish a model of carcinogenesis in fish, or from fish to humans?"

"The intent is to study the effect of chemicals in the environment and the etiology of cancer in fish. It includes the use of fish as a bioassay," Longfellow said.

Butel noted that having one expert on the study section would not be enough of an influence.

Adamson told the board that, "We could have a special study section, or we could add a couple of people to the regular study section. Do whatever you want, it doesn't make any difference to me which way you vote." He then left the room for most of the discussion.

Board member Allan Conney spoke in favor of the program announcement. "The more we know about carcinogenesis in a sentinel animal such as fish is a benefit," he said.

"I think the fish story is exciting," Barker said. She also favored a special study section.

Koprowski disagreed. "There is a certain danger in special sections. I would not vote for it. Soon, anyone will say that there is no specialist in their field on the study section and request a special study section. This happens at every study section, every day."

Barker noted that for the original RFA, a special study section was convened.

Fischer said there is not enough data to support the hypothesis that fish are a sentinel for human cancer.

"I would say they are sentinels for pollution," Longfellow said. For example, he said, there could be a pristine lake, but a study might find that all the fish have a certain cancer. That could lead to further investigation, which could turn up evidence that pollutants are being dumped into the lake.

"Would you support studies on whether fish can be sentinels for human cancer?" Fischer asked.

"That's premature," Longfellow said.

"But that is what this Board is interested in," Barker said.

Koprowski suggested that discussion be ended, and asked for a motion. Board member Pelayo Correa moved for approval. "If we don't have a special study section, the project will die," he said.

The concept was approved, with London and Roy Shore opposed.

Support services for clinical epidemiological studies. Recompetition of a contract held by Westat Inc. Four years, $1.748 million, proposed first year award $411,800.

This contract will provide support services for the clinical and field studies of cancer etiology and late effects of cancer treatment undertaken by the Clinical Epidemiology Branch, alone or in collaboration with other investigators. In addition, these support services will permit collection, processing and storage of appropriate biological specimens for laboratory studies of the biological mechanisms of cancer susceptibility.

The scientific direction and overall supervision for all projects are the responsibility of the staff of CEB. Support services provided by the contractor shall include: 1) preparation of data and collection forms, such as questionnaires and abstracting forms, with accompanying manuals; 2) assistance in enrollment of patients for study, interviewing, medical records abstracting, data and technical editing, collection and drawing of family pedigrees, and requesting hospital records, pathology reports and death certificates; 3) collection, processing, transport and record keeping for biological specimens; and 4) aid in data management, including data entry, proofing, editing, updating, records management, tabulations and statistical presentations.

CEB uses clinical observations to identify exceptional families that can yield insights into the etiology and pathogenesis of cancer. When patients are found, their clinical disorders are documented and specimens collected. CEB seeks collaboration with laboratory investigators, particularly NCI scientists. To collect data and specimens, the level of effort for support personnel shall include: professional staff, 1.5 person/year; laboratory technicians, 1.33; administrative, 1.5, and clerical-secretarial, 2. In addition, temporary field staff and support personnel will be hired for telephone interviewing, abstracting, coding and keying. Nonpersonnel costs include telephone charges, form printing, mailing, supplies and travel to sites of field work.

Branch studies in which the support services will be utilized are as follows: Studies of cancer prone patients, Mendelian traits predisposing to neoplasia, cancer survivors follow up, hepatitis B and liver cancer in veterans.

The concept was approved unanimously.

Breast cancer among women under the age of 45. Two years, total $1.8 million. Estimated first year award $975,000, competitive extension.

In May 1988, the DCE board approved a study of breast cancer among young women. Since then, three studies have been published which provide evidence of a positive link between oral contraceptives and breast cancer. These recent studies have raised questions regarding subgroup effects as well as whether the pill may merely advance the presentation of disease rather than being a true etiologic factor. As a result of these findings, there has been renewed interest in the relationship of oral contraceptives to breast cancer risk, and debate regarding the ability of our planned study to resolve these hypotheses. For a proper evaluation, an expansion of the study is necessary. This concept requests monies for recruitment of 500 additional cases under the age of 45, a sample of 500 older women and appropriate controls for these cases.

The original plans for the study included ascertainment of 1,000 breast cancers diagnosed among women under age 45 and an equal number of control subjects. In at least one center, identification of a random sample of community residents was sought to serve as a methodologic comparison for the main control series. This extension of the study will enable the detection of relative risks of 1.6 and 1.4 associated with four or more years of oral contraceptive use among nulliparous women and those with menarche prior to age 13. In addition, a sample of 500 women with breast cancer diagnosed at older ages is proposed to address the issue of whether oral contraceptives simply accelerate the diagnosis. To maximize the potential for evaluating methodological issues, these older subjects will be sought in areas that are selecting alternative controls. Thus, in addition to the approximately 2,335 subjects originally sought, funds are requested for an additional 2,665 study subjects, namely 500 cases under 45, 500 older cases, 1,000 random controls and 665 alternate controls. The study procedures would remain identical to those originally proposed. For a 20 percent sample of women, the study would attempt to validate histories of oral contraceptive usage against medical records to assess the possibility of recall bias.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-95196-42

Title: Smoking, Tobacco and Cancer Branch support services contract

Deadline: Aug. 14

This procurement is to provide the Smoking, Tobacco & Cancer Program with scientific, technical and logistical support services essential for the continuing development of intervention research in smoking prevention and cessation, and the dissemination of results from research trials. One award is anticipated and a five year incrementally funded cost reimbursement task order contract will be awarded.

This is a small business set aside, with a size standard of $3.5 million.

Contract Specialist: Joanne Feldman
RCB Executive Plaza South Rm 635
301/496-8603

The concept was approved unanimously.