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P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

HATCH HEARING TURNS UP FEW NEW DEFICIENCIES IN NCI CONTRACT MANAGEMENT; DEVITA BLASTED ON STRAUSS

The widely ballyhooed hearing by Sen. Orrin Hatch and his Committee on Labor & Human Resources on NCI contract management practices turned up little if any information on deficiencies not already aired thoroughly by the General Accounting Office and HHS Inspector

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In Brief

NCAB APPROVES CONCEPT OF CONVERTING BALTIMORE PROGRAM TO CANCER CENTER; NEW DCCP LABS NAMED

NATIONAL CANCER Advisory Board approved the concept of converting the Baltimore Cancer Research Program from an NCI intramural program to a cancer center affiliated with the Univ. of Maryland. An ad hoc committee will be established to review a grant application to support phasing in of the center; eventually it will have to compete for a cancer center core grant. . . . **CORRECTION**: The General Accounting Office did not blame alleged deficiencies in management of NCI's contract with Eppley Institute on failure of Congress and the White House to provide sufficient numbers of contract personnel as stated in ***The Cancer Letter*** (May 22). Congressman David Obey, commenting in 1978 on the GAO report, suggested that inadequate staffing was part of the problem and that Congress and the Nixon and Ford Administrations were jointly responsible for failing to give NCI enough positions. . . . **PROPOSED REORGANIZATION** of the Carcinogenesis Intramural Program in NCI's Div. of Cancer Cause & Prevention was spelled out by DCCP Acting Director Richard Adamson: Three new labs will be carved out of the Laboratory of Experimental Pathology—Human Carcinogenesis, to be headed by Curt Harris; Cellular Carcinogenesis & Tumor Promotion, headed by Stuart Yuspa; and Comparative Carcinogenesis, headed by Jerry Rice. Umberto Saffiotti will continue as chief of the Experimental Pathology lab and is in the process of moving to the Frederick Cancer Research Center. Another new lab, Molecular Oncology headed by George Vande Woude, also will be located at FCRC along with Rice's lab. George Todaro previously moved his Laboratory of Viral Carcinogenesis to FCRC. Snorri Thorgeirsson will move from the Div. of Cancer Treatment to head another new lab, Carcinogen Metabolism. Adamson quoted Winston Churchill in describing the changes: "This is not the end. It is not even the beginning of the end. It is only the end of the beginning." . . . **HOUSE SCIENCE** & Technology Committee's Subcommittee on Oversight plans to hold a hearing on the National Toxicology Program in July. Chaired by Congressman Albert Gore (D.-Tenn.), the subcommittee is interested in finding out how the multiagency program is working out.

SENATORS IGNORE IG, GAO COMMENTS THAT RECOMMENDATIONS WERE IMPLEMENTED

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General in their series of investigations over the last three years.

The hearing did elicit statements from representatives of both the GAO and Inspector General that NCI has implemented most of their recommendations and is making "noteworthy progress" in establishing strong contract management operations.

The hearing also demonstrated that both Hatch and Sen. Paula Hawkins (R.-Fla.), are having some difficulty in understanding the realities of the situation. Hawkins in particular seemed confused about grants and contracts, repeatedly criticizing NCI's contract management in a data falsification case which involved only grants.

Neither Hatch nor Hawkins were above stretching some points, and ignoring others, in obvious attempts to gain media attention. Some examples:

- Hatch permitted his staff to distribute copies of prepared testimony the day before the hearing, leading to nationwide publication of stories about "fraud, waste, mismanagement" in the Cancer Program. Few if any of the reporters noticed that the incidents were from old investigations rehashed in Hatch's statement, or that the IG prepared testimony ended with the comment that NCI had significantly improved its procedures. Most of the lay press and all of the radio and TV people had left when GAO's Edward Densmore said NCI had implemented most of its recommendations.
- Hawkins distributed a news release in which she said she was "outraged by evidence showing the National Cancer Institute awarded a contract to a researcher who was known to have falsified data." She was referring to Marc Strauss, now at New York Medical College, who has been accused (although not yet formally charged) of falsifying data on a protocol while doing clinical research at Boston Univ. for the Eastern Cooperative Oncology Group.

The ECOG work, of course, was supported by a grant. After he was forced to resign because of the charges, Strauss went to NYMC and competed successfully for an R01 grant from NCI to support a lab research project.

Hawkins' statement that Strauss is "known" to have falsified data is treading on thin ice. Strauss has vigorously denied the charges. An NIH investigation is under way and should be completed sometime during the summer. If a case cannot be proven against him either by the NIH probe or subsequent action, he may have the basis for a libel suit, not only against Hawkins but possibly the newspapers which may make similar statements.

Hawkins showed further confusion when she brought up the FDA charge that NCI was too slow in reporting renal toxicity from methyl CCNU, which was mentioned at the hearing of her Oversight Subcommittee two weeks ago. "I am alarmed that in spite of these warnings, the National Cancer Institute has failed to take steps to ensure the proper management of its contracting arrangements," she said.

The MeCCNU incident had nothing to do with contract management. Also, NCI Director Vincent DeVita at the Hawkins hearing had described the new arrangement with FDA which would speed up reporting of adverse reactions. He repeated it at the Hatch hearing, that reporting of the MeCCNU toxicity had been held up until an investigation established that the toxicity had occurred and was caused by the drug, the procedure previously worked out with FDA. The report to FDA will now be made immediately.

Hawkins also said that evidence produced at her hearing linked "at least one death to a failure to properly report side effects" of the drug. Not true—that death was the first instance of MeCCNU renal toxicity and brought on the investigation. There were no deaths reported while the investigation was in progress.

Hatch, Hawkins, and even Sen. Howard Metzenbaum were ferocious in their criticism of DeVita over the Strauss matter.

The falsifications in the ECOG study at BU became known when others on the staff there became suspicious and triggered an internal investigation which found such things as changing patients' birthdates to make them eligible for protocol entry, reporting of treatments and lab studies that were not done, and inventing a tumor in a patient who had none. ECOG Chairman Paul Carbone was informed, and he immediately dropped BU from all participation in the group. BU subsequently demanded and received Strauss' resignation.

Strauss received a very good priority score, in the 170s, when he applied for the R01. When it came before the National Cancer Advisory Board in January 1980, DeVita said he debated with himself on whether to inform the Board of the allegations against Strauss (the matter became public only when it was the subject of a superb series by the Boston Globe in July 1980). Because the grant involved no clinical work, and because "the grant was scientifically sound and Dr. Strauss was innocent until proven guilty," DeVita said he decided to let it go through without telling the Board.

"In hindsight, I realize that was a mistake," DeVita told the Hatch Committee.

Hatch, Hawkins and Metzenbaum demanded to know why DeVita was permitting funding of the grant to continue. The total amount was $910,000 for three years, and about a third has been paid. "These are pretty serious charges," Hatch said.

"They are serious and if true, reprehensible," DeVita said.

"I find it astounding that you are aware of these allegations and he still has a $910,000 grant," Hatch said. "In view of the fact that you knew most of these allegations, don't you think you should have withheld Dr. Strauss' grant until he had been cleared of the charges?"

"There was no system to handle that," DeVita answered. "I felt that we should give a person not proven guilty the benefit of the doubt. Under the debarment regulations we have now (implemented by NIH in the wake of the Strauss case), we certainly would have notified the Board."

Sen. Edward Kennedy (D.-Mass.) wondered if the Strauss case "is the tip of the iceberg or the iceberg itself."

"My opinion is that this is a rare situation," DeVita said.

"I'm not sure it is," Kennedy said, and referred to an investigation his (now defunct) Health Subcommittee had made which turned up instances of fraud in commercial testing of chemicals and drugs. Kennedy asked if DeVita planned to attend the meeting this week of the President's Ethics Commission in Boston, when Strauss will be asked to discuss the case. DeVita said, "I personally should not be there," saying NIH legal counsel has advised him to maintain some distance from the investigation since he may have to participate in judgment on its findings.

"It seems to me you're a little too blasé," Hatch said. "This matter is very serious. You're not running some little kiddy game. It worries me that you don't seem worried about it."

"I don't feel blasé. I'm waiting for the results of the investigation," DeVita answered.

"I don't follow you," Metzenbaum put in. "If you were in private business, you would not give a $900,000 contract to someone who had falsified data. You're not a jury. You're the director of the Cancer Institute. I share the chairman's concern. This requires dynamic leadership. I'm disappointed. How many other times do situations exist where you do not take dynamic leadership?"

Hawkins questioned the decision to give Strauss nearly $1 million for a grant while denying him access to investigational drugs.

"The issue at hand was patient safety," DeVita said.

"You are saying put this man in a lab, let him change something that may later be applied to the clinic. If he's not dealing with real humans, he's okay," Hawkins said.

"I share your discomfort," DeVita said. "I'm uncomfortable about drawing conclusions about a person under investigation, who has not been proven guilty, who has claimed others are responsible for the falsification, and who is an American taxpayer."

"The thing that bothers me the most is the attitude you seem to have," Metzenbaum persisted. "Somewhere you got the idea people are entitled to grants unless proven guilty. At what point can you say there's too many charges against this man, we're not going to spend any more until he proves he's not guilty?"

Bristling at Metzenbaum's charges of lack of leadership, but keeping his cool, DeVita said, "I'm not known as a subtle man. My colleagues are probably chuckling at the allegation I'm not forceful enough.... I'm not sure I could move in and stop the grant until Dr. Strauss is proven guilty."

NCAB OKAYS NEW SYSTEM FOR BYPASS BUDGET; $1.096 BILLION FOR FY 1983

Members of the National Cancer Advisory Board's Subcommittee on Planning & Budget were struggling this week with a new approach to the development of NCI's "bypass budget" for the 1983 fiscal year. Starting with a base figure intended to be considerably closer to the Administration's budget request, subcommittee members are attempting to fit their individual views of priorities into the budget.

The NCAB agreed to the new procedure at its recent meeting, accepting the subcommittee's recommendation. Director Vincent DeVita had asked the subcommittee to help develop a more realistic bypass budget and one in which priorities can be more clearly defined, with incremental increases listed on a program by program basis.

Subcommittee members received by mail a list of programs which they were asked to rank. They also may add others if they wish. Various options relating to priority score paylines and percentage figures were included. Responses were due back at NCI by mid-June, when the staff will attempt to translate those recommendations into a final budget which will be submitted directly to the White House, bypassing NIH and HHS.

Before it goes to the White House, all NCAB members will receive copies although it may be too late this year for the full Board to make any changes. A special meeting of the subcommittee may be required to wrap it up.

In the past, the bypass budget has started with a base figure of an increase for inflation over the previous year, usually about 12 percent, plus 5 percent to allow for modest growth. With the department budget in recent years requesting only increases of 1-2 percent for NCI, Director Vincent DeVita felt the disparity was so great that priorities in the bypass budget could not readily be fitted into the one eventually submitted to Congress.

The subcommittee recommended that a baseline budget of 7 percent over FY 1982 be used as the 1983 bypass figure. Since Congress has not yet estab-

lished the 1982 appropriation total, the 7 percent increase was based on President Reagan's request of $1.025 billion ($1 billion, 25 million).

Thus the 1983 fiscal year bypass budget will total $1 billion, 96 million. Under the old system, it would have been almost $1 billion, 200 million.

DeVita listed as examples of programs which could be identified for incremental increases as R01s, P01s, center core grants, training, clinical trials, and construction.

DCCP BOARD APPROVES PAYBACK SYSTEM FOR RESOURCES NOW PROVIDED AT NO COST

The NCI Div. of Cancer Cause & Prevention Board of Scientific Counselors last week approved implementation of a resources "payback" system which will require grantees, contractors and NCI (and other NIH) intramural investigators to pay for resources DCCP has provided at no charge in the past.

John Cole, DCCP acting program director for research resources (who is also program director for RNA virus studies [II]), described how the system will work in a series of questions and the answers he presented to the Board:

1. What is the "payback" system for resources?

The payback system is one in which the recipients of particular resource materials or services reimburse the resource contractor directly based on a price schedule agreed on between the NCI and the contractor. The contractor in turn credits these receipts against his costs which are shown on the monthly vouchers which he submits to the government for payment under the contract.

2. Why was the payback system initiated?

The payback system is a reflection of several phenomena; among them the shrinking budget of NCI, a perception that gratis distribution of resources did not always result in their most effective utilization, and a desire to see these resource dollars utilized by grantees and contractors included in a peer review system.

3. How will the payback system work?

There are two general modes under which we see the payback system operating. The first is exemplified by the contract for production and distribution of avian myeloblastosis virus and AMV reverse transcriptase which became effective on May 19, 1981. In this contract the cost reimbursement system will be imposed immediately since only about five of the over 600 users have requested amounts of the material in the past which would indicate that they would have financial problems in paying for future needs. The second mode would be applied where past needs indicate significant problems would be encountered by a number of investigators in paying for their resource needs. We would then propose to phase in the payback system in such a way that investigators would not have to unduly curtail their ongoing research efforts.

4. Who will pay for these resources?

A general rule is that grantees, contractors and intramural scientists will pay. There are several exceptions—distributions to investigators who receive resources under the special bilateral agreements between the United States and certain foreign countries. In addition gratis distribution of reduced amounts of materials may be authorized for grantees who are awaiting review of requests for supplements.

5. How are the prices set for the various resource materials?

The prices are arrived at by the process of negotiation between the government and the contractors. The government's two primary objectives are to provide the quality and quantity of materials needed by researchers at the lowest possible price and to cover, as much as possible, the actual costs of the contracts included under the system.

6. How was it decided when various contracts would be brought into the payback system?

It was felt that an appropriate time for this to take place would be at the time the contract is undergoing renewal. This offers an opportunity to phase in a number of contracts over an extended period of time so that the whole burden of the payback system would not fall upon the scientific community at one time. This should allow more time to seek the funds necessary to procure the services which they need to support their research activities.

7. Are there any types of contracts which are considered not appropriate for the payback system?

Yes, contracts in direct support of branch functions such as the BCB repository, computer support for the branch, and efforts of this nature are obviously not suitable for a payback mechanism. In addition, parts of certain contracts are not felt to be suitable. For example, the contract with Rush-Presbyterian St. Luke's Medical Center for the breeding of cotton-top marmosets also supports holding of these animals after they have been inoculated by various investigators. The holding part of the effort is an appropriate function of a payback system, but the portion of the contract devoted to the breeding is not.

8. Will the payback system result in immediate availability of dollars to be used for other purposes?

No. It is necessary under current procedures that the contracts be funded by the government in the first year. During this year, as proceeds are received from grantees, contractors or others, the proceeds will be subtracted from the government's obligation to fund the contract during the year's time. These funds will then be carried over into the second year of the contract and reduce the needs for funds in the second year. We would anticipate that some funds will be available in the second year and with proper management additional funds in the third year of a given contract.

NCI grantees who under past procedures would receive the resources at no charge will have to include the payback costs now in their grant applications. Supplemental grants will be available for ongoing grants. For contractors, payback costs will be negotiated in their contracts. Intramural users will have to provide for the payback costs in their budgets.

"Isn't this just an internal reshuffling of dollars?" Board member Barry Pierce asked. "I don't see where there is any savings."

"When they have to justify those costs at study section review, that may result in lesser amounts requested," Cole said. "We also receive requests from other government agencies, and from individuals funded with other than NCI funds, including foreign investigators not included in the bilateral agreements." Amounts NCI could recover from those users "could be substantial," Cole said.

"I wonder if anyone will use these resources if they have to pay for it," Board member Louis Siminovitch commented. Cole said a user survey indicated there would be continued demand, provided that supplements or in some cases gratis authorizations are available.

"But will you channel the savings back to R01s?" Board member Bernard Weinstein asked. "These resources have played a unique role for grantees. They are crucial to the small investigator. I'm concerned that in effect you are withdrawing resources from the extramural grant program."

"That is a wrong perception," DCCP Acting Director Richard Adamson said. "Money will be put into the grants program to pay for these costs, either through supplementals or in the original applications."

"Won't this increase the level of bureaucracy?" Pierce asked.

"No, it is reducing it," Adamson said.

"The proposal makes people more responsible for what they request," Siminovitch agreed. "At present, they are not responsible. I'm in sympathy with the proposal, but I'm nervous about Bernie's point, that study sections will not see the need for these materials."

"We'll go to the study sections and explain," Cole said.

"It challenges people, including our intramural people, to make more effective use of resources," Adamson said. "This is an experiment. If it doesn't work, we're prepared to scuttle it."

Weinstein said he would be willing to approve the system, "with the proviso that grantees be protected." The rest of the Board agreed.

The resources contracts which will be included in the initial implementation of the payback system are:

—Life Sciences Inc., for avian myelobastosis virus, AMV reverse transcriptase, and AMV myeloblasts. Payback amount estimated at $560,000. Immediate implementation. The 600 users receive an average of $450 worth of enzymes a year.

—Life Sciences, for Epstein-Barr virus, purified EBV DNA, and Raji cells. Payback amount, $315,000. Gradual phase in planned. Requests from Biological Carcinogenesis Branch grantees for larger amounts will require payment for the first $1,000 and the remainder either through administrative supplements or gratis distribution up to 50 percent of the amount previously received until an application for necessary funds can be subject to peer review.

—Life Sciences, for specific pathogen free white leghorn chickens, eggs and Japanese quail eggs. Payback $240,000. Implementation will be same as for the EBV contract.

—Becton-Dickenson, for antisera to oncogenic viruses and their protein components. Payback $400,000. Implementation same as for the EBV contract.

—Litton Bionetics, for a holding facility for primates inoculated with a variety of materials. Payback $425,000. Immediate implementation. Most users are intramural scientists.

—Child Research Center of Michigan, for cell culture identification services. Payback $160,000. Implementation same as for the EBV contract.

—Rush-Presbyterian St. Luke's, for breeding of cotton-topped marmosets and holding of experimental animals. Payback $310,000. Immediate implementation for the holding effort.

RFA NIH-NCI-DCCP-CPCB-81-1

Title: *Mechanisms of biological and chemical prevention of carcinogenesis*

Application Receipt Date: *Aug. 15*

The Div. of Cancer Cause & Prevention of NCI invites grant applications from interested investigators for studies on the mechanisms of inhibition of carcinogenesis. The proposed studies would seek, as their major objective, to enhance present understandings concerning the mechanisms of action of various agents.

Background

Strategies for cancer prevention involving reduction or elimination of human exposure to environmental carcinogens may not always be possible. Further, significant portions of the human cancer burden may be due to endogenous carcinogens, cocarcinogens and promoters. Inhibition of the development of cancer by administration of chemical, biochemical and biological compounds, which directly and/or indirectly inhibit the cancer producing effects of neoplastic and promoting substances, offers an alternate approach to cancer prevention.

Many studies on chemoprevention in experimental animal systems have already demonstrated the feasibility and relevance of this approach. A large number of compounds and substances have been shown to be effective chemopreventive agents against almost every major class of carcinogen in the prevention of carcinogenesis in organs comprising the majority of cancers in man. Among these are a variety of antioxidants, retinoids, protease inhibitors, flavonoids, coumarin and other lactones and disulfiram (and related compounds). However, very little is now known concerning the basic mechanisms of action of these chemopreventive agents. Similarly, recent evidence suggests that biological agents such as lymphokines may have significant anticarcinogenic potential.

The initiative of this RFA derives from the desire of NCI to encourage both basic and applied studies on the mechanisms of biological and chemical prevention of carcinogenesis. In this regard, there is an intended emphasis on mechanisms of anticarcinogenesis, or biological and chemoprophylaxis, as opposed to anticancer, or chemotherapy. Specifically, this intended emphasis is upon mechanisms of antipromotion (and/or antiprogression) of carcinogenesis, as well as upon mechanisms of inhibition of initiation and fixation.

Objectives and Scope

The research encompassed by the present RFA relates to both basic and applied studies intended to

provide insights and approaches to an understanding of mechanisms of inhibition of carcinogenesis. The proposed studies would seek to enhance such knowledge with respect to the following categories of biological and chemical agents:

Category 1: Antioxidants, flavonoids, disulfiram and related compounds, nucleophiles, including cellular nucleophiles such as glutathione, and other physiological trapping agents, and coumarins and other lactones.

These chemically diverse inhibitors appear to act by preventing carcinogens from reaching or reacting with critical target sites, when given prior to and/or simultaneously with exposure to neoplastic substances. Inhibition of tumorigenesis at many organ sites has been demonstrated, such as liver and lung, large and small intestine, breast, skin, bladder and forestomach. Proposed research might include (but by no means be restricted to) studies on effects of these inhibitors on cellular activation and detoxification systems, the role of free radical scavengers and the superoxide dismutases in chemoprevention, inhibitor-induced changes in cellular permeability or transport of carcinogens, competitive inhibition for carcinogen receptors, inhibitor structure/activity relationships, and inhibitor metabolism.

Category 2: Vitamins, provitamins and other cofactors.

The role of the vitamins, provitamins (such as the carotenoids) and other cofactors in chemoprevention is largely unknown. Vitamins A, C, E and B2 (riboflavin) have been reported as inhibitors of carcinogenesis, while the first three named (A, C and E) have been reported to inhibit tumor initiation. Many vitamin A analogs are known to act as anti-promoters of phorbol-ester promoted, DMBA-initiated skin tumorogenesis; and beta-carotene (a precursor to vitamin A having vitamin A activity) inhibits skin tumorigenesis initiated by DMBA and promoted by croton oil, as well as skin tumors induced by repeated UV exposure. On the other hand, carotenoids lacking vitamin A activity are effective only against UV-induced skin tumorigenesis.

In cell culture, vitamin A suppresses malignant and phenotypic transformation caused by chemical and physical carcinogens or by transforming polypeptides; and recent results indicate that vitamin C can not only inhibit progression of methylcholanthrene induced transformation in vitro, but also cause morphologic reversion of transformed cells to the normal phenotype.

Proposed research might include (but by no means be restricted to) the biochemical interactions of these compounds among themselves and with other substances, as for example with selenium and the selenoenzymes such as glutathione peroxidase; effects on other systems of glutathione metabolism; studies on mechanisms of inhibition of chemical and physical transformation and carcinogenesis; effects on composition and structure of cellular membranes, on differentiation and growth, and on tissue subcellular distribution of these agents and changes in carcinogenesis; binding proteins; molecular sites of action; regulation of gene expression; clarification of enhancing and inhibiting effects on mutagenesis; role in oxidative metabolism; modification of cytotoxicity; and interactions with endocrine and immunological systems leading to inhibition or suppression of the carcinogenic process.

Category 3: Retinoids.

These compounds have been shown to effectively inhibit cancer development in bladder, breast, skin and respiratory tract in experimental animals, and to suppress malignant and phenotypic transformation in vitro whether caused by chemical carcinogens, ionizing radiation or polypeptide transforming factors derived from virally transformed cells. Additional studies are particularly needed in such areas as: retinoid metabolism, pharmacokinetics and structure/activity relationships; retinoid binding proteins; molecular mechanisms of retinoid action; effects of retinoids on cellular differentiation; effects of retinoids on membrane topology, cell surface biochemistry, cellular interactions, and biochemical processes linked to carcinogenesis.

Category 4: Protease inhibitors.

These compounds have been shown to inhibit tumorigenesis in skin, colon, esophagus and mammary gland; suppress both radiation-induced and chemical carcinogen-induced transformation in culture; and inhibit both UV- and carcinogen-induced bacterial mutangenesis. Proposed research might include (but by no means be restricted to) effects of protease inhibitors on the cell surface, DNA synthesis, growth control mechanisms, and gene activation and repression.

Category 5: Biological agents such as chalones, lymphokines/lymphotoxins and tumor necrosis factors.

Recent data indicates that lymphokine/lymphotoxin preparations possess anticarcinogenic in addition to anticancer activity. The potential for prevention of development of cancer and the exploration of the biological and biochemical mechanisms involved, requires increased and deeper investigation for this and other biological agents such as chalones and tumor necrosis factors, including preparations of animal and human origin. Research on isolation, purification and biochemical identification is needed, as well as determination of the species, organ sites and cell types against which anticarcinogenic activity exists, in addition to fundamental investigations of mechanisms of action.

Further, combination chemoprevention or combined biological and chemical prevention of carcino-

genesis presents a new, virtually unexplored area for studies on the inhibition of the carcinogenic process(es). Several recent investigations have demonstrated the feasibility of this important approach.

In this regard, it should be emphasized that the interest of NCI in mechanisms of inhibition of carcinogenesis (that is, in this RFA) ranges from the most early events associated with initiation and fixation through early and later stages of promotion, progression and expression of malignancy.

An understanding of the mechanisms which underlie successful intervention at one or more stages of the carcinogenic process by one or more agents is obviously of great importance. In this regard, applications proposing use of one of the chemicals/agents indicated above in combination with a chemical (e.g., anti-inflammatory agent), factor (e.g., anti-tumor growth factor) or biological agent (e.g., normal human globulins, interferon) not so indicated will be considered acceptable applications, in addition to those proposing use of more than one of the substances which are listed above.

Mechanims of Support

This RFA will use the traditional NIH grant-in-aid. Responsibility for the planning, direction and execution of the proposed research will be solely that of the applicant. The total project period for applications submitted in response to the present RFA should not exceed three years. The intent is to fund multiple projects, with total costs amounting to approximately $2 million for the first year. This funding level is depending on the receipt of a sufficient number of applications of high scientific merit.

Method of Applying

Applications should be submitted on form PHS-398, the application form for research project grants. Application kits are available at most institutional business offices, or may be obtained from the Div. of Research Grants, NIH. The words "Proposal in Response to RFA NIH-NCI-DCCP-CPCB-81-1, Mechanisms of Biological and Chemical Prevention of Carcinogenesis" must be typed in bold letters across the face page of the application.

The completed original application and six copies should be sent or delivered to: Div. of Research Grants, NIH, Westwood Bldg. Rm 240, 5333 Westbard Ave., Bethesda, Md. 20205.

A copy of the application should also be sent, and inquiries may be directed to: Dr. Carl Smith, Chemical & Physical Carcinogenesis Branch, DCCP-NCI, Landow Bldg. Rm 8C-37, Bethesda, Md. 20205. Phone 301-496-4141.

RFA NIH-NIEHS-EP-81-3

Title: *Immunotoxicology of environmental agents*
Application Receipt Date: *Aug. 1*

Although it is known that a variety of drugs and chemicals as well as ionizing radiation and altered nutritional states can influence the immune system, little definitive information is available concerning the effects of a wide variety of environmental agents on immunologic homeostasis. Undesirable effects resulting from the interaction of environmental agents and the immune system can be manifested as immunodeficient disease or immunopathology resulting from an adverse response of the immune defense mechanism.

There is increasing evidence that chronic low-dose exposure to agents in the environment, including heavy metals and chlorinated hydrocarbons, can depress immune responsiveness and may, in some cases, increase susceptibility of animals to infection. The relevance of these findings for human disease is unknown and additional information on the basic mechanisms of immunopathologic reactions and their detection is needed.

Objective of this announcement is to indicate that the National Institute of Environmental Health Sciences has an interest in supporting high quality research in areas of immunotoxicology which will elucidate the role of environmental agents in producing adverse effects on the immune system.

Although all areas of research which will contribute to an understanding of the mechanims of action of these agents will be considered, emphasis is placed on the development and validation of immunologic methods and host resistance models to study the effects of chemicals of environmental concern on the immune response.

In order to accomplish the goals of the program, the following areas of research have been identified for priority consideration:

1. The development and validation of viral, bacterial or tumor susceptibility models to better define alterations in host resistance following subchronic chemical exposure.
2. The application of tests of immune function to study changes in the immune response following exposure to chemicals of environmental concern.
3. The development of immunological and biochemical methods to define the effects of chemicals of environmental concern on macrophage function.
4. The potential of microsomal enzyme activation systems coupled with in vitro immune function assays as a novel approach to screen chemicals for immune alteration.
5. The examination of bone marrow progenitor cells as targets for chemical induced immunotoxicity.
6. The development of animal models to study the potentials of chemicals to induce hypersensitization and allergy.
7. Studies to examine the effect of inhalation exposure of chemicals on the functional integrity of the immune elements of the lung.

The RFA identifies the scope of NIEHS' interest but does not require that the proposal conform to a specific research protocol. Thus it is expected that each successful applicant will plan, direct and carry out the research program. As with any research grant, recipient must obtain prior approval for any major change in the scope or objectives of the approved project. Applicants should be aware that this general requirement is particularly pertinent when, as in the case of RFA solicitations, the awarding Institute has committed funds in response to a specific program need.

It is anticipated that $600,000 will be allocated for this program during the first year; however, award of grants is contingent upon the availability of funds. The project period should adequately reflect the time required to accomplish the stated goals and be consistent with the NIH policy for grant support.

Applications should be submitted on form PHS-398, and sent to DRG, as noted in the RFA above. The face page of this application should be labeled "In Response to RFA NIH-NIEHS-EP-81-3." One copy of the application should be sent to: Dr. Edward Gardner Jr., Regular Research Programs Section, Scientific Programs Branch, Extramural Programs, National Institutes of Enviornmental Health Sciences, P.O. Box 12233, Research Triangle Park, N.C. 27709.

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. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

SOURCES SOUGHT SYNOPSIS 18

Title: *Production and maintenance of specific-pathogen-free (SPF) animals for cancer research*

Deadline for Receipt of Qualification Statements: *June 16*

The Japanese quail and white leghorn chickens must be maintained under strict environmentally controlled conditions which preclude infestation by parasites and pathogenic microorganisms including viruses. The meaning of the term specific pathogen free here is that of the birds, both white leghorn chickens and Japanese quail, are free of the following avian pathogens: Mycoplasma synoviae; mycoplasma gallispecticum; salmonella pullorum; Rous sarcoma virus; Marek's disease, herpes virus; infectious bronchitis virus; chicken embryo lethal orphan virus.

In addition, the SPF chicken embryos must also be tested for their phenotype (C/O, C/A, C/AB, C/BE, etc.) and the animals must be tested for the presence of Rous accessary virus one and Rouse accessary virus two.

The contractor shall produce and characterize approximately: 10,000 C/E, 700 C/O, 50 C/AB fertile white leghorn chicken eggs, 3,000 embryonated eggs and 200 young chicks and approximately 19,200 fertile Japanese quail eggs, 1,600 embryonated eggs and 100 young quail. The contractor shall ship these materials as directed by NCI to various investigators.

This is not a request for proposal. NCI wishes to receive statements of interest in and qualifications for providing germfree and SPF avian material. Invited to respond are organizations which have the capabilities and experience to perform the work described above. Organizations' capabilities will be evaluated on their capability to provide the above services as evidenced by the following types of information which must be provided:

1. Facilities–The contractor must have immediately available upon initiation of the contract appropriate facilities and specialized equipment, adequately contained in the biohazard and environmental control sense, for large scale production of these SPF animals under barrier conditions which will not compromise their defined status. 2. A listing of previous contracts or work performed in propagation of chickens and quail under SPF conditions including experience in quality control and shipping. 3. Capabilities of principal investigator–Provide a description of individual's previous experience and capabilities for production and characterization of avian species maintained under SPF conditions and specifically address prior experience in monitoring these animals for bacteria, viruses and phenotypic expression of desired traits (C/E, C/O etc.). 4. Availability of or your plans for immediate acquisition of an SPF flock of Japanese quail which can produce approximately 20,000 eggs per year.

NCI will evaluate qualification statements and will issue an RFP to those firms jusged to have superior qualifications.

Contract Officer: Elizabeth Osinski
RCB Blair Bldg Rm. 117
301-427-8888

The Cancer Letter _Editor Jerry D. Boyd

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