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NCI FUNDING PLAN FOR 1983: 20% CUT FROM RECOMMENDED LEVELS FOR ALL GRANTS, CHANGE IN PROGRAM PROJECTS

Are the days of funding NIH and NCI grants at the full levels recommended by study sections gone forever?

Perhaps not, but it does not seem likely they will be fully funded in

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In Brief

SUBCOMMITTEE OKAYS $980 MILLION FOR NCI IN 1983, HOUSE PASSES WAXMAN BILL, WITH CENTERS LINE ITEM

HOUSE HEALTH Appropriations Subcommittee added $25 million to President Reagan's budget request of $955 million for NCI in the current (1983) fiscal year. That would amount to a 2.2 percent increase over the 1982 budget of $943 million. Congress adjourned to Nov. 29 after approving a continuing resolution that provides interim funding for federal agencies through Dec. 15, with spending held to the 1982 level. The Senate Health Appropriations Subcommittee did not mark up its bill before adjournment; both houses will have to rush all appropriations bills through the lame duck session. . . . **THE HOUSE** passed the Waxman bill reauthorizing health research, including NIH and renewing the National Cancer Act. It authorizes an 11 percent increase in NCI's budget; includes a line item authorization for cancer center core grants, at $83 million for the first year; athorizes $66 million for cancer control; provides explicit authority for clinical cancer education programs; authorizes a new National Arthritis Institute; calls for the National Academy of Sciences to undertake a study of NIH's structure; and provides for closer congressional oversight of NIH programs. HHS does not support the Waxman bill, and Congressman Edward Madigan (R.-Ill.) told the House that the President would veto it if it comes through the conference with the Senate in its present form. Meanwhile, the Senate version was marked up by Sen. Orrin Hatch's Labor & Human Resources Committee but did not reach the floor—another item for the lame ducks. It authorizes a six percent increase; authorizes $58 million for cancer control; includes language re-emphasizing the Senate's interest in the International Cancer Research Data Bank, and adding emphasis on research in continuing care; increases from $35,000 to $50,000 the size of grants (direct costs) which may be awarded by the NCI director without approval of the National Cancer Advisory Board; permits center core grants for up to five years; establishes procedures for grants appeals. The Senate bill does not include the centers line item or clinical education authority. Lobbying has continued for amendments to be offered on the floor to override the NCAB and continue the Organ Site Program essentially as it is, perhaps with the addition of breast cancer as a fifth site; and the clinical education programs.

NO GRANT WOULD GET LESS THAN 1982 LEVEL, INTRAMURAL HELD TO 4% GROWTH

(Continued from page 1)

the current, 1983, fiscal year, and probably will not be until the economy improves and/or Congress and the White House can be persuaded to provide more money for biomedical research.

Since NCI has had to exist with a level budget starting in 1980, it has had to impose some reductions in center core grants, cooperative groups, and program projects. During the 1982 fiscal year just ended, cuts were made across the board, including traditional (R01) grants, and for the first time in many years, in noncompeting grants, also including R01s.

The situation will not improve in 1983, unless Congress adds substantially to the President's budget request, and the President allows any increase to stand without vetoes or rescisions.

NCI Director Vincent DeVita told the National Cancer Advisory Board Monday how the institute plans to fund grants in 1983 if the President's budget of $955 million stands:

- All grants—new, competing renewals, noncompeting renewals, program projects, centers, cooperative groups—would be reduced 20 percent from the recommended levels.
- In the case of renewal grants, if the 20 percent reduction would put them below current levels, the cuts would only go down to the current level. No grant would receive less than it got in 1982.
- Program directors, with the concurrence of NCI division directors, could approve variations of 10 percent for individual grants.
- Money spent through contracts will be reduced by five percent.
- The intramural budget will be limited to a four percent growth.

This plan would allow NCI to fund 750 grants, including transfer of 20 from the Organ Site Program, if NCI is permitted to follow the plan for revamping that program and bring those grants into the R01/-P01 pool.

"The priority score cutoff will be different," DeVita said. "There is a lot of compression in those scores." He noted that as budgets have become tighter throughout NIH, individual study sections have tended to score grant applications higher, in order to make the grants in their particular disciplines more competitive with the others and more likely to be funded. With so many grants bunched together in scores, the responsibility of determining which are funded and which are not gravitates to the program directors. "I don't believe the study sections understand that," DeVita said.

With that compression, it is possible the cutoff score this year will be around 160.

Although NCI received a 2.2 percent increase over its 1982 budget in the bill marked up by the House Health Appropriations Subcommittee (See In Brief), DeVita pointed out the percentage was substantially less than that for the rest of NIH. "That is not a generous increase. The tendency to make our increases smaller is a reaction to the time when our budget grew so fast. It does not recognize that we are tightly managed, and that we have some major commitments."

NCI has managed to squeak through without crippling major programs through tighter management, phaseout of lower priority programs and of those which have accomplished their missions, and drastic reductions in contracts. But that can be carried only so far.

"We can't keep all our programs intact through 1984 if we continue to get small percentage increases," DeVita said.

The 1983 funding plan also will require some substantial changes in the handling of program projects, including modification of review. The changes will be controversial, DeVita said.

The most important change will deal with the practice of program project review committees in deleting projects within grant applications which they consider weaker or of lesser importance. The committees then score the revised application, which of course gets a better score than it would with the weaker elements included.

Some members of the scientific community have objected to that practice as unfair and inappropriate. Their objections have been heeded; here is how DeVita said the problem will be addressed:

—A letter of intent will be required before a program project application is submitted.

—Review committees will be required to score each project within a grant application as submitted, and the final score will be the average of them all. They will not be permitted to delete projects.

DeVita acknowledged that some problems remain to be resolved. One is how to weight individual projects within a grant. He asked NCAB member Maureen Henderson to chair a committee to develop a weighting system.

"The end result may be that P01 grants will become smaller, and there will be fewer of them," DeVita said. He hopes to implement the new system in time for P01s which will be awarded at the May, 1983, NCAB meeting, and the deadline for those applications will be in January.

FCRF CONTRACTS TOTAL $40.3 MILLION, LIBRARY SERVICES AWARD ANNOUNCED

"We have lived up to our agreement with the National Cancer Advisory Board to reduce the size of the Frederick contract," NCI Director Vincent DeVita told the NCAB Monday. Minutes later, NCI

Associate Director Peter Fischinger, who is scientific coordinator for the Frederick Cancer Research Facility, described the five new contracts awarded for operation of the facility and revealed they would total $40,363,019 in the 1983 fiscal year.

The highest total the recently but not totally displaced Litton Bionetics Inc. ever received was $30 million. So how could a 33 percent increase be a reduction, a reduction the NCAB had demanded be in the range of 20 percent?

The answer, of course, is that since the decision was made to trim the FCRF operations by 20 percent, NCI has moved some of its intramural laboratories to the facility, some from quarters on the NIH campus (where they were forced out by the closing of some old buildings for renovation), some from contractor provided space in the Washington D.C. suburbs. Overhead costs, supplies, and some support staff formerly paid by NCI to the NIH management fund or to the contractors all are included now for those labs in the new FCRF contracts.

Fischinger, DeVita, and other NCI executives have made considerable effort to explain to critics of the huge FCRF Litton Bionetics contract why more is less, that reductions really were made, and that additional costs added to the contract represent only a transfer of funds and not money coming out of the extramural or grants pools.

Before NCI (and a few other NIH) labs were moved to FCRF, the contract with Litton totaled about $25 million. That has been reduced over the past three years to the point where, if it were not for costs of the transferred labs, it would be a little more than $16 million.

The labs transferred from NIH are being operated at FCRF at no additional cost, Fischinger told the NCAB. Those moving from contract facilities around Washington will be operated at Frederick at a savings of about 25 percent.

The massive recompetition of the FCRF contract, split into five because, when it was recompeted in 1976, no one wanted to go up against Litton Bionetics for the entire job, was the largest and most complicated of its kind in the history of NIH. The contract with Program Resources Inc. for operations and technical support, at $30.1 million, is the largest single contract ever awarded by NIH.

The final contract to be awarded was for scientific library services, which went to Data Management Services Inc., of Frederick (the other four were announced previously, ***The Cancer Letter,*** Aug. 27 and Sept. 17). All the contracts were awarded for five years.

Program Resources, of Rockville, Md., was the biggest winner. Growth of the company, founded in 1973 and headed by Richard White, has been phenomenal. A year ago, the company was grossing about $4 million a year. Additional contracts the firm landed during the year doubled that figure, and the FCRF contract will put it out of sight.

Four of the five contracts provide for profits to be paid through an award fee system. The basic research program, as it has in the past, will pay a fixed fee to the contractor, still Litton Bionetics.

The award fee system places an amount equal to seven percent of the contract figure into a pool. Twice a year, monitors and coordinators will report to an award fee board which will determine how much of the money in the pool the contractor deserves as a profit. An award of 50 percent of the available money would be considered good, although Litton averaged about 70 percent during its 10 years of running the entire operation.

The system would put $2.1 million in the award pool for PRI during the year, and the company could earn from $1 million to $1.5 million, or even more if the board determines its performance exceeded Litton's.

The award fee board is made up of some NCI division directors and deputy or associate directors.

Approximately $28.3 million of the $30.1 million in PRI's contract supports NCI activities; the remainder is paid for by other NIH components, labs of the National Institute of Neurological & Communicative Disorders & Stroke, and the National Institute of Allergy & Infectious Diseases.

The new contracts will permit an escalation of a total of 10 percent over the five years, which would lift the total amount to nearly $45 million.

Raymond Gilden, who was director of the Biological Carcinogenesis Program for Litton Bionetics, has moved over to PRI as director of Frederick operations.

PRI's responsibilities under the contract include:

1. Providing central scientific resources and services to NCI scientists located both at FCRF and at NIH and to contractor scientists in the LBI-operated Basic Research Program at FCRF. These activities include chemical synthesis and analysis; biological products such as viruses, growth factors, and monoclonal antibodies; electron microscopy; and quality control of tissue cultures.

2. Supporting the Biological Response Modifiers Program of NCI's Div. of Cancer Treatment. This program includes an oncology center at the Frederick Memorial Hospital and associated research at FCRF.

3. Operating a large scale fermentation facility for development and production of anticancer drugs and biological agents to support programs in the Div. of Cancer Treatment.

4. Providing technical support for laboratory animal research, including management of holding areas, operation of an animal health diagnostic laboratory, operation of a histopathology laboratory and provision of expertise in laboratory animal medicine.

5. Managing and developing safety and security

programs to ensure the protection of workers and the environment. This includes technical support to the NIH Div. of Safety.

6. Providing administrative and business services for all five contractors, including acquisition of materials, supplies, and equipment.

7. Renovating and maintaining the FCRF complex.

The new contract with Litton Bionetics for the basic research program will total $7,268,810.

It will support research in molecular genetics and genetic engineering, protein and nucleic acid chemistry, oncogenic viruses, physical and chemical carcinogenesis, immunology, and the physical characteristics and the biology of cancer cells.

Michael Hanna, who had headed the entire operation at FCRF, has left to become director of the Litton Institute of Applied Biology. J.L. Liverman is acting principal investigator for the contract, and Isaiah (Josh) Fidler, director of the Cancer Metastasis & Treatment Laboratory, is acting director.

Harland Sprague Dawley Inc., of Indianapolis, won the contract for animal production, totaling $1,655,097 for the first year. The firm will produce the small animals used for research at FCRF, at other NCI labs, and for other NCI contractors and grantees.

Information Management Services Inc., Rockville, won the computer services contract, amounting to $774,066 for the first year. The company will operate the comprehensive automated processing facility there. Paul Young is the program manager.

Data Management Services' contract for the library totals $557,206 for the first year.

Dividing the work into five contracts accomplished the goal of stimulating competition, for the most part and for the big ticket jobs. Litton Bionetics had to compete against Johns Hopkins Univ. and Program Resources for the basic research contract. PRI, although its proposal (as well as Hopkins') was considered in the competitive range, withdrew it before the final selection was made.

Litton, PRI and one other firm seeking the operations support contract were in the competitive range; five were in the competitive range for the computer contract; and three were in the competitive range for the animal production contract. However, only one of the library proposals, that of the winner, of course, was considered in the competitive range.

All proposals were reviewed by technical review committees, with final evaluation made by the NCI Executive Committee minus DeVita and Fischinger. The Executive Committee is made up of the NCI deputy director, the division directors, and the executive officer.

All five contracts will run through Sept. 25, 1987. The first contract to Litton Bionetics was awarded in 1972.

SOME NCI RESPONSES TO CCOP LETTERS MISSING; NCAB ARGUES PEDIATRIC ISSUE

The Postal Service, or someone, has dropped the ball in getting NCI's responses to the 232 organizations which submitted letters of intent on the Community Clinical Oncology Program.

Jerome Yates, associate director in the Div. of Resources, Centers & Community Activities which is managing CCOP, said that it appears as many as 20 percent of the responses drafted by Program Director Robert Frelick have not been received, three to four weeks after they were sent out.

Yates suggested that anyone who submitted a letter of intent and who has not received a reply should contact Frelick immediately by phone. His number is 301-427-8708.

A conference for CCOP business representatives has been scheduled for NIH on Oct. 13. It will be held in Masur Auditorium, which is in the Clinical Center, rather than Wilson Hall as previously announced, starting at 9 a.m.

Yates appeared Monday at the meeting of the National Cancer Advisory Board to present an update on the program and to field questions from some Board members who have been contacted by persons concerned that CCOP will damage pediatric oncology.

"I've had a tremendous number of phone calls from people asking to keep (handling of pediatric patients) as it is," Board member Ann Landers said.

Victor Braren, new member of the Board who is a pediatric urologist at Vanderbilt Univ., had distributed a memo to other members expressing some of the concerns.

Critics seemed most worried about the prospect that CCOP would mean the end of the relationship of the two pediatric cooperative groups—Childrens Cancer Study Group and the Pediatric Oncology Group—with hospitals participating in the Cooperative Group Cancer Control Program. That program has assisted community hospitals in developing relationships with cooperative groups and encouraging participation of their patients in clinical trials conducted by the groups.

There had been some speculation that CCOP would supercede the Cooperative Group Cancer Control Program, but NCI later decided there would be room for both. But hospitals participating in the latter could switch to CCOP and would have to give up their membership, which some CCSG and POG members feel could disrupt the existing relationships. CCOPs could have other research base affiliations.

Braren said, "Unfortunately, the mechanism (CCOP) will work very poorly for pediatric oncology. . . . Basically, pediatric patients would to some degree be swallowed in adult programs because, in all settings so designed under CCOP, adult patients would vastly outnumber pediatric patients. Some of

the proposals in CCOP are already being carried out in the current cancer control mechanism for pediatrics. Community physicians and community hospitals are currently involved in ongoing relationships with university based pediatric oncologists in the care of pediatric patients with cancer."

NCI Director Vincent DeVita said, "We're on the same wave length. Pediatric patients are being very well handled, and I would just as soon not include them in CCOP."

However, five or six of the letters of intent were from organizations intending to establish pediatric CCOPs, which would complicate the situation if NCI were to exclude those organizations now.

Braren offered a motion to exclude pediatric groups from CCOP. Board members Robert Hickey and Gale Katterhagen objected. "I don't think this is a threat to POG or CCSG," Hickey said. "A sweeping motion against it would not be in the best interests of anyone."

"Has the NCAB ever modified an RFA after its release?" Katterhagen asked.

DeVita said that since the Board does have the authority to approve or disapprove grants after initial review, if the members feel they do not want pediatrics included, it would save time to do the modification now.

"My thought is not to cut off pediatric CCOPs, but to discourage them," Braren said.

"This discussion sets the tone. The word will get out," DeVita said.

Barbara Bynum, director of the Div. of Extramural Activities, objected to the motion, saying, "An RFA is on the street, to which five groups have responded in good faith."

"Half of all pediatric patients are on protocols, and the present system works well," Katterhagen said. "But to change an RFA is something else."

Braren said he would modify his motion, to go on record against combining pediatric and adult CCOPs. But Sheldon Samuels suggested that rather than a formal motion, the Board could exercise its prerogative when reviewing the grants and make sure that "swallowing up" does not occur.

Maureen Henderson and LaSalle Leffall also objected to the motion. DeVita said, "There's not any disagreement here. We hear what you are saying."

Landers, saying that she had to catch a plane, said, "I withdraw the motion" as she went out the door.

"She didn't make the motion," Hickey said.

"I made it and I withdraw it," said William Powers, who had offered a substitute to Braren's. Other members agreed, and the subject was dropped.

NCI CONTRACT AWARDS

Title: Mayo lung project for detection and localization of early lung cancer, continuation

Contractor: Mayo Foundation, $1,971,798.

NTP BOARD APPROVES CONCEPT OF FOUR NEW CONTRACTS, TWO RECOMPETITIONS

The National Toxicology Program Board of Scientific Counselors has given concept approval to four new contract supported projects and two recompetitions totaling an estimated $1.9 million in first year funding.

Three of the four proposed new projects possibly could go to other government agencies through interagency agreements. RFPs will be issued if NTP decides to compete them.

The new projects are:

Validation of two in vitro teratogenesis prescreening systems. Estimated first year funding, $300,000. Mechanism: two research contracts, two years. Staff narrative:

The use of an in vitro prescreening system for teratogens will serve to: 1) improve the criteria for the selection of chemicals which should be tested in whole animal systems and for assigning priorities to testing chemicals; 2) decrease the need for expanded whole animal testing initiatives; 3) accelerate the rate at which chemicals are evaluated; 4) improve the breadth of data on teratogenic potential for chemicals; 5) use actual human target tissue when appropriate and available and 6) decrease testing costs. While we do not expect to replace whole animal testing systems with an in vitro teratogenesis screen, we do expect to improve the selection of chemicals for whole animal testing.

We will validate two in vitro screening systems for teratogenesis. The in vitro testing systems will allow us to assign priorities to chemicals for conventional teratology testing. These screening systems will decrease the pressure on whole animal testing in teratology and increase cost effectiveness of our testing activities. This validation effort is seen as the first of a series of in vitro testing initiatives in reproductive and developmental toxicology.

We will validate both the tumor cell attachment inhibition assay and the human palatal mesenchyme cell growth inhibition assay. Both assays would be run simultaneously at two testing laboratories and approximately 50 chemicals will be selected for the validation of the protocols. The chemicals will be chosen from a list of teratogens and non-teratogens which is being developed by a group of teratologists under the auspices of Kate Smith of EPA and Gary Kimmel at NCTR. A repository will be established from which the chemicals will be analyzed for purity and stability before shipment. All chemicals will be coded and tested blind by the contractors. We have selected two cell culture systems which will be validated. The first system evaluates the ability of chemicals to inhibit ascites mouse ovarian tumor cell attachment to concanavalin A-coated disks (Braun, A.G. et al., Proc. Natl. Acad. Sci. USA, 79: 2056-2060, 1982). The working hypothesis behind this system is that certain teratogens may interfere with cell-cell interactions; the testing system models these cell-cell interactions by studying lectin-mediated cell attachment and the potential of chemicals to interfere with that attachment.

Preliminary studies on 102 known teratogens or generally accepted non-teratogens demonstrated a 79 percent accuracy in assessing activity (Braun, supra). Many of the teratogens not identified in the cell attachment assay, however, were identified by the second proposed testing system which uses human embryonic palatal mesenchyme (fibroblastic) cells (Pratt, R.M., et al., Teratogen. Carcinogen. Mutagen., 1982, in press). This system, which was developed at NIEHS, has taken the false negatives from the cell attachment assay and demonstrated a positive response in 12 out of 13 instances. This system measures the growth inhibition of the potential

mesenchymal cells in culture. This test system involves an embryonic cell line derived from the human palate which is often malformed in the human embryo and, therefore, these cells may be uniquely sensitive human embryonic tissues. It has already been shown to be complimentary to the tumor cell attachment assay. When the two systems are combined they demonstrate greater than 90 percent accuracy in predicting teratogenicity.

Increased tumor incidence in the offspring of mutagen treated mice. Estimated first year funding, $200,000. Mechanism: research contract or interagency agreement, four years.

The project is designed to investigate tumor frequencies in the offspring of mice treated with known germ cell mutagens. The primary purpose of the project is to improve ability to predict the impact of induced germ cell mutations on human health by investigating a mouse system in which cancer incidence is observed in the first generation following mutagen exposure.

Human genetic risk estimations are based preferably on mammalian germ cell mutagenesis studies. Systems presently available detect recessive mutations resulting in either visible phenotypic changes, such as coat color or enzyme activity/-electrophoretic mobility changes. These assays are well suited for determining induced mutation rates. However, to predict human health effects from an increased rate of recessive mutations requires major assumptions that diminish the confidence that can be placed in the resulting risk estimates.

In order to more accurately assess the health effects that might result from human exposure to germ cell mutagens, it is necessary to develop animal systems that detect effects directly related to human disease states and that are expressed in the first generations following exposure to a mutagenic agent.

The case for conducting this proposed study with cancer as the genetic endpoint is supported by several lines of evidence. First, the fact that the risk of cancer in humans is strongly influenced by genetic factors is well established. McKusick lists at least 30 dominantly inherited predispositions to cancer. Rearrangements in chromosome structure and aneuploidy are known to predispose to cancer. Genetic diseases that affect DNA repair processes or chromosome stability also result in increased risks of cancer.

The initial phase of the proposed study would be designed to confirm the phenomenon of cancer resulting from germ cell mutations in mice. With regard to earlier studies, Nomura's experiments did not employ the most effective germ cell mutagens and the animals were sacrificed too early (eight months) to obtain complete tumor information. Tomatis employed an extremely effective mutagen (N-ethyl-N-nitrosourea or ENU) but at a suboptimal dose and then tested germ cell stages that are not demonstrated to be sensitive to mutation induction by ENU. The proposed experiments would maximize the probability of observing an effect by using B6C3F1 mice on which the most is known about spontaneous tumor incidences, would employ a dose of ENU known to induce extremely high frequencies of mutations, would test germ cell stages with demonstrated sensitivity to ENU, and would allow animals to be followed for up to two years for tumor frequency.

If these experiments confirm the phenomenon of increased tumor frequency in the offspring of mutagen treated parents, additional studies would be conducted. One of the first would be an investigation of the relationship between mutation frequency and the frequency of tumors. This would be accomplished by determining both mutation rates and tumor frequencies in the same F_1 populations. Such information would be needed in order to predict tumor frequency from a determined induced mutation frequency. Further studies could be conducted to extend the observations to germ cell mutagens other than ENU.

Ultimately it would be desirable to conduct experiments to determine if progeny of mutagen treated parents are more susceptible to chemically induced cancers and whether such susceptibility is concomitant with or independent of a predisposition to spontaneous tumors.

The genotoxic evaluation of potentially hazardous chemicals in the in vivo-in vitro UDS rat hepatocyte assay. Estimated first year award, $380,000. Mechanism: research contract or interagency agreement, three years.

This proposal recommends a study to develop the in vivo-in vitro UDS rat hepatocyte system as an assay to identify hepatocarcinogenic and hepatotoxic chemical agents among those chemicals that may be potentially hazardous to human health. This short term assay has the advantage of combining the elements of metabolic capability and chemical disposition in the intact animal with the sensitivity of the DNA repair endpoint detected in cultured rat hepatocytes.

The in vivo-in vitro UDS rat hepatocyte assay measures chemically induced UDS in the liver following exposure of rats to the test chemical. This in vivo-in vitro system offers an advantage over the in vitro hepatocyte assay in that the normal metabolic components of chemical disposition can be expressed in the intact animal. In addition, the sensitivity of the assay is greatly increased because the repair response—the incorporation of ^{3}H-thymidine into DNA—is measured in the induced target organ cells in vitro. Although the number of chemicals that has been tested in the in vivo-in vitro UDS rat hepatocyte assay is relatively small, this assay has been shown to be responsive to direct acting mutagens and genotoxic hepatocarcinogens of several different classes of chemicals. Representative chemicals from the nitrosamines, aromatic amines, nitroaromatics, and mycotoxins induce a strong UDS response. Chemicals that are not hepatocarcinogens, however, generally are not active in the assay, even though they may induce tumors in other target organs. In addition, it would be expected that nongenotoxic agents which may be cocarcinogens or tumor promoters would also not elicit a UDS response in this assay.

The proposed study combines the enhanced sensitivity of an in vitro study with the advantages of normal chemical disposition in the intact animal. The assay is most likely to detect genotoxic chemicals that are either hepatocarcinogens or hepatotoxins.

The objective is to test approximately 40 chemicals per year for FY 1983, 1984, and 1985, for a total of 120 chemicals. The test chemicals will be selected on the following basis:

1. Those 20-25 chemicals which are candidates each year for the NTP chronic assay.
2. The other 15-20 chemicals will be selected from either those chemicals which are of known hepatocarcinogenic activity in the NTP bioassay or from other chemicals of priority interest to NTP.

Assay of chemically induced gene transposition in Drosophila. Estimated first year award, $150,000. Mechanism: research contract or interagency agreement, three years.

The possible existence of mobile gene elements was recognized over 25 years ago by Barbara McClintock in studies with maize; subsequently other transposable genetic elements which can insert into different chromosomal sites and which can alter gene expression have been defined. It has further been shown that the mobile gene elements may be principally derived from repetitive DNA sequences which occur in all eucaryotic genomes. It is possible that through the restructuring of chromosomes, via the movement of the elements, new patterns of sequence expression arise. Recent technical advances have fostered intensive investigation of these elements which show remarkable degrees of conservation of the organization in a variety of different species. Additional interest in

the potential importance of transposable elements has occurred from the speculation (Cairns, J., Nature, 289: 353, 1981) that human cancers may be the result of genetic transpositions.

The mdg (mobile dispersed genetic) elements of Drosophila are a well defined set of transposable elements which show the potential for many integration sites, together with structural features of direct or inverted terminal repeats. Key features of the mdg elements have been described (Shapiro, J.A. and Cordell, B., Bio. Cell, 43: 31, 1982); however, at the present time virtually nothing is known about the potential of chemicals to induce transposition, how such processes might work, or the best way to search for them. Extensive development will be required to know whether or not this system should be adapted to widespread testing of chemicals.

There are some indications that a high proportion of mutations occurring in the wild (i.e., not under tightly controlled laboratory conditions) are the result of transposition of moderately repeated DNA sequences. Whether these are induced by any environmental agents is unclear although there is some preliminary evidence in Drosophila that chemical mutagens increase the frequency of transposition (see Rasmuson, et al. Mutation Research, 54: 33-38, 1978). If this is the case, the testing protocol used to detect chemically induced mutations in Drosophila may be missing a sizeable class of induced mutations. It is possible that some chemical mutagens act exclusively by the production of transpositions and therefore would not be identified under existing protocols and this possibility must be examined.

It is necessary to use specific molecular probes to identify specific transposable elements and their recombination, and it is proposed that the initial phase of the work be directed to the study of the w (white eye) locus which is known to be a site of transposition. Part of the test development will be to show that changes (at w) were due to transpositions where specific phenotypic change may be indicative of such transposition.

Important questions which must be answered are: 1) is the resulting phenotype due to specific insertion of excision of the mobile element; 2) should male or females be treated; 3) should larvae or adults be treated; 4) what spectrum of mutagens can we expect to identify; 5) does the assay give "positives" with "non-mutagenic" analogs; and 6) does the assay detect "non-mutagenic" carcinogens.

The two recompetitions are:

Drosophila mutagenesis testing. Estimated first year award, $270,000. Mechanism: resource contracts, four years.

In September 1979, four year contracts were awarded to Bowling Green State Univ. (Dr. Ron Woodruff), Brown Univ. (Dr. Stan Zimmering) and the Univ. of Wisconsin (Madison) (Drs. Ruby Valencia and Seymour Abrahamson) to test chemicals for mutagenicity in Drosophila melanogaster. These contracts are scheduled to terminate in September 1983.

Drosophila is a valuable test organism because it has many of the same chemical metabolizing enzymes found in mammals, it can provide information on the types, frequencies and germ-cell specificity of induced mutations (such as recessive lethals and translocations) and can demonstrate that the induced mutations are passed along to future generations through the germ cells.

All chemicals are tested by feeding for the sex-linked recessive lethal test; non-mutagenic chemicals are retested using injection. Chemicals producing sex-linked recessive lethal mutations are tested for their ability to induce reciprocal translocations by the same route of administration. The initial stage of the contracts was the standardization of the protocol and an investigation of the usability of various non-aqueous vehicles for feeding and injection of chemicals insoluble in water. The solvents selected were DMSO and ethanol for both feeding and injection, and vegetable oil for injection of the highly insoluble chemicals.

To date a total of 71 samples has been tested; at the termination of these contracts approximately 130 samples will have been tested. The test results are being entered into a computerized data base. Manuscripts which present the test data and analyses of the data are in preparation.

Chemicals selected for testing in Drosophila are those which are positive or equivocal in Salmonella. Chemicals not mutagenic in Salmonella but belonging to chemical classes which have not been previously reported in Drosophila will also be tested, along with selected negatives from other classes. Additionally, chemicals are nominated for Drosophila testing by the NTP Chemical Evaluation Committee as part of a genetic toxicology screen.

Continuation of these contracts will allow the NTP to develop a data base on Drosophila mutagenicity which can be matched against Salmonella, in vitro, and in vivo mammalian cell mutagenesis and cytogenetics results, and carcinogenesis results, in an attempt to determine the predictive and correlative values of this test.

In vitro cytogenetics testing. Estimatedfirst year award, $580,000. Mechanism: resource contracts, four years.

In September 1979, four year contracts were awarded to Columbia Univ. (Dr. Arthur Bloom) and Litton Bionetics Inc. (Dr. Sheila Galloway) to standardize a protocol and test chemicals for their ability to induce chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) in cultured Chinese hamster ovary (CHO) cells. These contracts are due to terminate in September 1983.

Both laboratories started with cells from the same clone and after an initial trial with control chemicals, tested 11 coded chemicals. The initial protocol yielded results that were consistent and reproducible between the laboratories. Since that time, the laboratories have tested chemicals under code at the rate of approximately 30 per year per lab.

In September 1981, in order to increase the number of chemicals being tested, a contract was awarded to Environmental Health Research and Testing Inc. (Dr. P.S. Sabharwal). This contractor is using the same cell line and protocol developed by the original two laboratories.

To date, a total of 97 samples have been tested by Columbia and Litton, with an additional eight completed by Environmental Health Research and Testing Inc. At the termination of these contracts a total of approximately 190 samples will have been tested. All test results are being entered into a computerized data base. In addition, statistical approaches (in collaboration with Dr. Barry Margolin, BRAP, NIEHS and Dr.

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

The dollar estimates listed with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

Phil Archer, Univ. of Colorado) to the evaluation of both the CA and SCE data are being developed. Once these statistical approaches are finalized, all data will be reanalyzed.

Chemicals tested for their ability to induce CAs and SCEs include those which are being considered for carcinogenicity or heritable mutagenicity testing, chemicals of interest based upon their mutagenicity in other test systems and/or their reported carcinogenicity, and chemicals which are being studied in order to develop structure-activity information. Randomly selected chemicals are tested in more than one laboratory as a quality control check of reproducibility.

Continuation of the in vitro cytogenetics testing program will allow the NTP to increase the number of chemicals tested and will result in the formation of a unique and unparalleled data base which can be used by NTP personnel and other researchers for structure-activity studies, comparative mutagenicity studies and mutagenicity-carcinogenicity correlations. The individual data will be useful in making decisions on chemicals to be tested for carcinogenicity, mutagenicity or other toxicological endpoints and in the interpretation of carcinogenicity data.

The Board also approved the concept of an interagency agreement for development of an assay system to determine if mammalian transposable gene elements are targets for toxic environmental agents. It would cost an estimated $300,000 in the first year of a four year agreement.

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.

RFP 23-83-6002

Title: *Demonstration service project to monitor radiation therapy quality assurance by mailed review*

Deadline: *Approximately Nov. 15*

Demonstrate a quality assurance service to small facilities not serviced by a center for radiological physics and to demonstrate that there is an advantage to knowing an outside check of one's performance, even if only mail, is being made. Prospective contractors must meet the following minimum requirements:

1. Prospective contractors shall have a fully functioning TLD System in place and shall be performing, or recently performed, mailed TLD measurement.

2. The calibration system for the TLD shall have been tested and an error analysis performed on the entire mailable system showing an overall accuracy better than 5 percent. (Inherent in this process is the evaluation of supralinearity and fading effects on the TLD).

3. Prospective contractors shall have available a film developer and densitometer.

DHHS/Public Health Service
Food & Drug Administration HFA-511
5600 Fishers Ln., Rm 12A-05
Rockville, Md. 20857
Contact: Jacquelyn Carey, 301-443-4420

RFP NCI-CN-35011-46

Title: *Support to the Smoking, Cancer & Health Programs*

Deadline: *Dec. 6*

The Div. of Resources, Centers & Community Activities, NCI, is seeking proposals for provision of all necessary personnel, labor, facilities and equipment, not otherwise provided by the government, to provide necessary technical support to the Smoking, Cancer & Health Programs in the conduct of scientific conferences, meetings and workshops; report documentation and editorial services; technical document development; liaison and data management, analysis and processing.

The successful offeror will be required to have this facility located with 35 miles of the NIH campus in Bethesda, Md. Other minimum facility, equipment and personnel requirements are included in the request for proposal.

This procurement is a 100 percent set-aside for small businesses. For purposes of this procurement, a small business is classified as small if its average annual gross receipts for the preceding three fiscal years do not exceed $2 million. A small business "concern" means any business entity organized for profit with a place of business located in the United States.

Contract Specialist: Deborah Castle
RCB, Blair Bldg. Rm 2A07
301-427-8745

NCI CONTRACT AWARDS

Title: Facility for preparing and housing virus-infected intact and chimeric mice

Contractor: Bioqual Inc., Rockville, Md., $861,569.

Title: Use of multiple markers in the diagnosis of lung cancer

Contractors: Harbor-UCLA Medical Center, $262,895; Univ. of California (San Diego), $171,887; Sloan-Kettering Institute for Cancer Research, $260,022.

The Cancer Letter Editor Jerry D. Boyd

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