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"FORWARD FUNDING" WILL COST NCI $38 MILLION, 270 GRANTS, AS OMB LEGALLY IMPOUNDS FY 1985 MONEY

The Office of Management & Budget's strategy to cut more than $200 million from the NIH 1985 fiscal year grants budget without violating antiimpoundment laws became clear last week when the news was leaked that the White House intended to order "forward funding" of enough new and competing renewal grants to reduce the number

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In Brief

BOSTON HOTEL OFFERS FREE ROOMS TO CANCER PATIENTS; SMOKING PROGRAM REPORT AVAILABLE

FREE ROOMS for out of town cancer patients being treated in Boston hospitals will be made available by the Westin Hotel. The offer extends to an accompanying family member or, when the patient is a child, to both parents, for up to three weeks. The program is being administered by the Massachusetts Div. of the American Cancer Society.... **ANNUAL REPORT** of NCI's Smoking, Tobacco & Cancer Program for 1983 is now available free from Prospect Associates, Suite 401, 2115 E. Jefferson St., Rockville, Md. 20852. The report reflects NCI's "heightened commitment to the prevention and control of cancer through more defined, targeted and concerted intervention research" as well as continued focus on the basic toxicologic and carcinogenic aspects of tobacco use, according to Joseph Cullen, deputy director of the Div. of Cancer Prevention & Control.... **AMERICAN CANCER** Society Board Chairman Robert Gadberry, President Robert McKenna and Public Issues Committee Chairman Gerald Murphy will appear Feb. 4 at a hearing scheduled by Sen. Paula Hawkins (R.-Fla.) on FDA's handling of anticancer drug INDs.... **HUMAN POPULATIONS** which consume seeds (rice, corn, beans, etc.) have lower incidences of breast, colon and prostate cancers, NYU Institute of Environmental Medicine investigators Walter Troll, Krystyna Frenkel and Rakoma Wiesner noted in an editorial in "Journal of NCI" December issue. They hypothesize that the cancer preventive constituents of seeds are protease inhibitors which are uniformly present in all seeds, perhaps to discourage consumption by insects.... **CORRECTION:** Contract awarded to Nancy Low & Associates for technical support services for NCI's Office of International Affairs is for five years, not 38 months as reported in last week's issue of **The Cancer Letter.** The contract, for $1.75 million, is for marketing and promotion programs to present OIA's services to potential users. These include technical information services, on line research information data bases, professional journals, monographs, the monthly Cancergrams, and PDQ. Informatics General Corp., which held the contract for the previous three years, will provide additional technical support as a subcontractor to Low.

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FORWARD FUNDING, LEVEL 1986 BUDGET, CANCER ACT RENEWAL PROBLEMS FOR NCI

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funded to 5,000. That is the number originally requested by the Administration, 1,500 less than provided for by Congress in the 1985 appropriations bill which was signed by President Reagan.

Forward funding is the practice of obligating money for the full costs of multiyear grants in the first year of the awards. Thus, three year grants would be paid for all three years from 1985 appropriations, although the funds would be made available only at the usual time. The second and third years would not be a burden on the federal budgets of those years.

The immediate effect would be to cut that amount needed to fund the second and third years from this year's NIH budget. Assuming that the cuts would be applied evenly across all institutes, NCI's share would be more than $38 million, with a reduction in the number of NCI RO1 and PO1 grants of about 270. The payline for NCI grants in FY 1985, previously estimated at 270, would be slashed to 260.

Since the figure of 5,000 new and competing grants which the Administration has attempted to apply to NIH has been limited to "research project" grants, that has been interpreted to mean the traditional RO1 and program project (PO1) grants. This particular action does not affect center core grants, cooperative agreements, training grants or other special categories.

The OMB strategy appears to be completely legal, although certainly contrary to the intent of Congress as expressed in the appropriations bill and accompanying reports. "It's an ingenious way of getting around the intent of Congress and apparently is entirely within the law," a spokesman for the Assn. of American Medical Colleges said. AAMC led the fight in 1973 against impoundment of about a half billion dollars of health funds by President Nixon. AAMC took the Administration to court and won release of the money; Congress later passed the Congressional Budget & Impoundment Control Act which established a formal procedure by which the President can withhold appropriated funds. That procedure involves obtaining concurrence of both houses of Congress before appropriated money can be impounded.

Apparently, no legal challenge is possible this time. It is possible for Congress to pass a 1985 supplemental appropriations bill and include language specifically forbidding forward funding. More likely, the House and Senate Appropriations Committees will attempt to make it up in the 1986 appropriations bill, hearings on which will start later this month. The 1986 bill possibly could include strong language aimed at forcing OMB to comply with the intent of Congress. The upcoming hearings are likely to be even more vitriolic than they were last year, when it appeared NIH was willing to sacrifice centers in order to fund 5,000 grants (Congress, as NIH knew all along, did not accept that proposal, which gave committee members a fine opportunity to blast the Administration).

The Administration's 1986 fiscal year budget is scheduled to go to Congress Feb. 4. It will not contain much, if any, of the extra money called for in the NCI bypass budget needed to get the ball rolling on the Year 2000 goals. The White House has decided to hold NIH to 1985 levels in its request—about $350 million less for NCI than the bypass figure. The hearing on NCI's budget by Congressman William Natcher's House Labor-HHS Appropriations Subcommittee will be held sometime during the first two weeks of March.

Meanwhile, NCI is even more concerned about renewal of the National Cancer Act than the budget.

Director Vincent DeVita took the unusual step of closing an hour of the meeting Monday of the Div. of Cancer Prevention & Control Board of Scientific Counselors to talk about the 1986 budget, the forward funding ploy and NIH reauthorization legislation, which would include renewal of the Cancer Act.

A reauthorization bill was passed by Congress last year but vetoed by the President. For the most part it continued NCI's special authorities, including the bypass budget, the President's Cancer Panel, presidential appointment of the director and members of the National Cancer Advisory Board, and the cancer centers and cancer control programs. But it did not explicitly provide for renewal of NCI's authority to conduct its own peer review of contracts and grants other than RO1s, or to appoint members to its advisory groups and review panels. Without that authority, the review and appointment power would revert to the NIH director, who could delegate it back to NCI if he chose to do so.

The authority to do most of its own grant and contract review, without the delays and other hassles involved in going through NIH, may have been the most important provision in the National Cancer Act. Along with the right to appoint members of the review committees, that permitted NCI and its advisors to establish the direction of the Cancer Program and its elements, set priorities and move quickly when new opportunities arose, without interference from forces at NIH not familiar with nor sympathetic to Cancer Program needs.

Budget and reauthorization problems probably will be discussed at the next meeting of the President's Cancer Panel Feb. 25 at Wistar Institute.

DCPC BOARD OKAYS ONE FEASIBILITY STUDY FOR LOW FAT DIET, DELAYS OTHER

The Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control gave permission for one of two controversial breast cancer low fat diet trials to start accruing participants in a feasibility study but delayed the start of the other because of alleged deficiencies on the part of the nutrition coordinating unit.

The Board voted approval at its meeting this week for the low fat diet, high risk breast cancer prevention study to get under way. A report will be made to the Board in September on whether a full scale, long term followup study is feasible, as demonstrated (or not) in the six month study. If the Board of Scientific Counselors agrees that it is feasible, that decision will be presented to the National Cancer Advisory Board in October for its concurrence.

The stage 2 breast cancer trial, in which patients will be randomized to a low fat diet or their usual diets following surgery, will be delayed for up to 60 days, Board members agreed. DCPC staff and the Board's Advisory Committee for Low Fat Diet Trials recommended the delay when, they reported, the nutrition coordinating unit at the Univ. of Minnesota was unable to develop required materials for the study which met approval of staff and the committee.

The DCPC Board and the NCAB previously had gone along with the two studies with considerable reluctance, with some members skeptical of the ability of investigators to obtain sufficient compliance with diets or to adequately monitor compliance. The protocols call for diets which average 20 per cent of calories from fats; the normal American diet includes 40 per cent calories from fats.

The studies were initiated upon the recommendation of Ernst Wynder, president of the American Health Foundation and a proponent of the theory that high fat diets increase the incidence of breast cancer. Wynder has pointed to lower incidences of breast cancer, and lower rates of recurrence in breast cancer patients, in Japan, where the diet is close to the 20 per cent fat level.

Because of the cost (at least $15 million over the full length of the studies) and the questions raised, the Board insisted on feasibility studies before committing NCI to the full program.

Each study is starting with three institutions participating as clinical centers, a nutrition coordinator and statistical coordinator. The stage 2 study will five more clinical centers if it goes into the full implementation; the high risk study will have a total of 13 clinical centers.

Clinical centers in the stage 2 feasibility study are Baylor Univ., with William Insull as principal investigator; Univ. of Iowa, with Peter Jochimsen as PI; and Emory Univ., Daniel Nixon, PI. The statistical Center is at UCLA, with Robert Elashoff as PI. The troubled (according to NCI and the Board committee) nutrition center is at the Univ. of Minnesota, with Marilyn Buzzard as PI.

If the stage 2 trial goes into full implementation, the other clinical centers will be at Harbor-UCLA Medical Center, Rowan Chelbowski, PI; Illinois Cancer Council, Edward Scanlon, PI; American Health Foundation, Ernst Wynder, PI; Univ. of Pittsburgh, Bernard Fisher, PI; and New England Deaconess Hospital, George Blackburn, PI.

The nutrition unit for the high risk trial is at New England Medical Center, with Sherwood Gorback as principal investigator. The statistical center is at Fred Hutchinson Cancer Research Center, with Ross Prentice PI. The three clinical centers in the feasibility study are Baylor, with Insull as PI; Univ. of Cincinnati Medical Center, Myron Moskowitz, PI; and the Hutchinson Cancer Center, Maureen Henderson, PI.

If the high risk trial goes into full implementation, the other clinical centers will be at UCLA Jonsson Comprehensive Cancer Center, David Heber, PI; Roswell Park Memorial Institute, Curtis Mettlin, PI; Univ. of Pittsburgh, Bernard Fisher, PI; Cancer Research Center, Columbia, Mo., Ralph Reynolds, PI; Univ. of Miami, David Schapira, PI; Merrit Peralta Medical Center Kaiser Foundation Hospitals, Portland, Andrew Glass, PI; Univ. of Alabama, Albert Oberman, PI; Univ. of Iowa, Donald Young, PI; and Univ. of North Carolina, James Newsome, PI.

William DeWys, DCPC associate director and director of the Prevention Program, described development of the two studies and problems with the Minnesota nutrition unit. However, Board member Robert Cooper, chairman of the Policy Advisory Committee, pointed out that the program is being supported through cooperative agreements with the participating institutions and thus are grants. He said that the committee recommended unanimously that funding for the Minnesota nutrition coordinating unit be suspended immediately, pending a review of the problems by NCI and the committee which should be completed within 60 days.

Further discussion of the problems would not be "fair due process to the people involved. I suggest that the best thing to do, to protect the interests of the grantees and offer them due process, would be to accept the committee's recommendations and let the committee proceed with the review." Cooper argued that representatives of the Minnesota group should be present at any further discussion of their problems.

"One of the advantages of a grant is the opportunity to succeed and the opportunity to fail," Cooper said. "It is not appropriate to discuss this at length because it does jeopardize the rights of the grantee."

Board Chairman Barbara Hulka at first said she would "hesitate to ask the Board to vote on the recommendations without a discussion." However, she changed her mind after DeWys suggested that another controversial issue—whether adjuvant chemotherapy should be included in the treatment arm—be separated from the issue of suspending the coordinating unit's funding. Hulka agreed, and called for the vote on Cooper's motion to suspend funding. It was approved without dissent, although Board members Jerome DeCosse and John Ultmann abstained.

DeWys said that at a meeting of the principal investigators last summer, the issue of chemotherapy was discussed "exhaustively. Present were people very knowledgeable about chemotherapy and breast cancer, including Dr. Bernard Fisher. The decision was to include chemotherapy." However, a subset of investigators later reopened the issue.

Jerome Yates, DCPC associate director and director of the Centers & Community Oncology Program, commented that patient accrual might be a problem if chemotherapy is not offered. Yates said that the scientific basis for adjuvant chemotherapy for postmenopausal breast cancer patients has not been established, although for some subsets it has seemed to be beneficial. Yates cited a study by the Karolinska Institute in which postmenopausal patients were randomized to chemotherapy or tamoxifen, and chemotherapy was found not effective. Yates mentioned a review of 10,000 patients in various trials which found that 10-15 per cent of postmenopausal patients had responded to chemotherapy. "The question is, is it appropriate to expose 100 per cent of women to chemotherapy when only 10-15 per cent will benefit?"

Yates suggested that with ER and PR assays as part of the protocol, "you could make a case to treat them differently."

"I would back up Jerry's point," Board member Virgil Loeb commented. "You can define a subset of postmenopausal patients at high risk for recurrence. The evidence is lacking that others would benefit from chemotherapy."

Board member Lewis Kuller argued, "If chemotherapy is relatively ineffective, it would be a randomized variable and would have little effect on the outcome of the trial. It's a political question. Should NCI recommend that some women not get chemotherapy? I don't think that's a wise decision. It would be interpreted that NCI thinks chemotherapy for postmenopausal patients is not effective."

"Chemotherapy for postmenopausal patients is still experimental," Yates said. "I don't think it should be standard therapy. If we put it in all the arms of the study, we're saying we think it is standard therapy." He also noted that side effects of chemotherapy, particularly nausea and vomiting, could cause "all kinds of problems when you are introducing new diets."

Board member Charles Cobau agreed that chemotherapy for postmenopausal patients should not be considered standard treatment. "But from the point of view of this study, if it is confounded by the presence of tamoxifen or chemotherapy, it might be impossible to interpret."

"It's a real game in a study design to eliminate chemotherapy," DeCosse said. "If you give any chemotherapy, there is no end of variables. I have my doubts about its long term effectiveness. We have to keep in mind the importance of this feasibility study. The real concern is, will women stay on the diet? That is the key, the number one question when we look at this a year from now. Can it be done? That is the question that counts."

"The problem I see is the accrual rate," Wynder said. "It's okay to do without chemotherapy, but people read the New York Times when it says chemotherapy is good (and conclude that) not prescribing it is tantamount to malpractice."

Hulka said that she did not intend to ask for any motions now "on how the groups will conduct the trials," and there was no dissent, leaving the issue for the moment in the hands of the Policy Committee.

Insull, who addressed the Board Monday, said the investigators "were all a bit shocked by the amount of funds awarded. There were squeaks and squeals. We are in the process of making estimates on what we can do with the money awarded."

Wynder said he preferred to consider the stage 2 study a "nutrition adjuvant trial. We need to look at nutrition the same way we do chemotherapy... We have invited experts to develop ways to encourage compliance over the long term. We need to bring in the husbands, and to develop marketing strategies, the way MacDonald's sells hamburgers." He noted that a Big Mac contains 40 grams of fat, "all that we are permitting our patients to have for an entire day."

Wynder added that he hoped the stage 2 trial could be conducted without chemotherapy.

The high risk breast cancer prevention study will involve women determined at risk primarily on the basis of a familial or personal history of breast cancer. The feasibility study will involve 120 participants in the control group. They will have only two clinic visits, one for a baseline at the start and the other at the end of the trial. There will be no intervention, with passive observation.

There will be 180 participants in he intervention arm, divided equally between two groups. In one group, participants will have 22 sessions at the clinic over nine months; in the other, 15 sessions in nine months. Initial instruction will involve eight weekly sessions and two individual sessions in three months. After that, maintenance will involve twice monthly group sessions with one or two individual sessions as indicated, in the first group; one a month group sessions for the second group.

Monitoring will be maintained through diet records, questionnaires, and plasma cholesterol measurements.

DCPC BOARD APPROVES CONCEPTS FOR $26.5 MILLION IN CONTRACT PROJECTS

Concepts for contract supported research and resource projects which could total as high as $26.5 million over the three to five year life of the awards were approved this week by the Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control.

The Board tabled a concept proposal for two to four contracts for lung cancer risk factor intervention and followup studies with an estimated total cost of $3 million over five years.

By far the most extensive and expensive of the projects approved will be the development of community smoking cessation programs for heavy smokers. The contracts will support a coordinating center and five to eight participating centers. DCPC staff estimated the cost of the program at $2 million to $4 million a year over five years.

Staff description and Board discussion of the concepts follow:

Community smoking cessation program for heavy smokers. One coordinating center award, five to eight participating centers. Estimated cost, $2-4 million a year, five years, plus $200,000 for a nine month phase 1 development effort.

Goal of this program is to design and implement a community based study which will effectively recruit, retain and aid heavy smokers to achieve smoking cessation.

The overall prevalence of cigarette smoking in the U.S. has decreased from 43 per cent to 32 per cent over the last 19 years. However, these gains in cessation appear to be primarily in light and moderate smokers (i.e. <25 cigarettes per day); the proportion of smokers smoking more than 25 cigarettes per day has increased during this period from 26 to 37 per cent in males and 13 to 25 per cent in females. The cancer risk among heavy smokers is substantial; relative risks from the major prospective studies for smokers of more than 25 cigarettes per day range from about 12 to 23. Although heavy smokers represent only about 30 per cent of all smokers, they account for about 45 per cent of lung cancers among smokers. Although the risk for lung cancer is a strong function of both duration of smoking and amount smoked, the benefits of cessation are considerable even in heavy smokers. Relative risks for lung cancer 15 or more years after cessation for these smokers decreased substantially. Increasing cessation in heavy smokers represents a key component in the effort to achieve a 50 per cent reduction in cancer mortality by the year 2000. Despite the significant disease burden incurred by the heavy smoker and the potential for greatly reduced risk after cessation, this group of smokers has not been intensively targeted by public health research programs.

In general, observational studies of large populations (such as the VA Normative Aging Study and the Framingham Study) indicate that quit rates decrease as the number of cigarettes smoked at baseline increases. Among the few intervention studies not hampered by weak design or insufficient power, increasing cessation success for heavier smokers has been found to correlate with increasing intensity of intervention. In the MRFIT, for example, where multiple and intensive individually oriented interventions were used, long term cessation rates for heavier smokers were greater than those in any study of that size, although cessation rates were considerably less than that of lighter smokers (19 per cent vs. 39 per cent at six years--cohort analysis).

A promising approach to the heavy smoker problem is through the community. The multipronged approaches possible in community based interventions can provide intensity and pervasiveness of the smoking cessation message. This is not possible with laboratory based programs which deal with the individual in isolation from his social milieu. The idea of using the community as the focus for an intervention trial has been advanced by a number of leading researchers and practitioners. By a "community intervention trial" is meant interventions directed at achieving behavior change in large groups of people by working through the multiple social influences that determine health habits. Examples of social influences are school, home, workplace and community sites. This approach more effectively generates peer group influence, which is an important determinant of smoking cessation success. It also mobilizes community involvement, including mechanisms for self perpetuation of the interventions. Observations from ongoing studies indicate that community interventions affect not only individuals who choose to enroll in a particular program, but also influence those not formally enrolled.

Community wide intervention trials differ from the traditional clinical trial model in which individuals are randomized to either a treatment or a control condition. In a community trial, larger social units such as towns or neighborhoods are the units of randomization. Use of social units permits the comparison of interventions which operate not on the level of individuals, but upon social structures. It is this alteration in social systems which is increasingly considered to be the most

feasible way to effect the large changes in society required to reduce the life style risk factors associated with cancer. Cancer control interventions which make changes on the organizational and social level thus have a potential for risk reduction not possible with interventions delivered solely on an individual by individual basis. In addition to greater generalizability, the community based approach is also more cost effective.

A number of community based interventions have been funded by the National Heart, Lung & Blood Institute. The proposed research will build upon these first generation studies, but will differ in a number of ways, including: a special emphasis on the heavy smoker; increased power and improved design; use of newer intervention packages; concentration of resources on one risk factor rather than multiple factors; emphasis on collection of cost effectiveness data necessary to plan subsequent translation to large scale public health applications.

The objective of the proposed research is to develop a community based intervention program that will have four principal outcome measures: 1. Extent of program implementation. 2. Extent of heavy smoker participation. 3. Heavy smoker quit attempts. 4. Heavy smoker cessation. Although the primary goal is to improve cessation rates in the heavy smoker, light and moderate smokers will not be excluded.

Pairs of matched communities will be selected and randomly assigned to either a control or experimental condition. The target population range of communities is from 50,000 to 250,000; this could include portions of major metropolitan areas. Census data indicate that 50 per cent of the U.S. population lives in communities of this size. The experimental condition includes a hierarchy of standardized interventions of increasing intensity ranging from mass media approaches to individually focused treatments. Population changes in smoking will be assessed by cross sectional prevalence surveys as well as by following cohorts of representative smokers. It is expected that the trial would be implemented in five to eight pairs of communities.

Since many questions remain about the relative efficacy of different interventions for heavy smokers (e.g. media, individual counseling, nicotine gum, contests, self help strategies), the basic design will be expanded by the nesting of additive experimental interventions within treatment communities. This involves a two step randomization process. The primary randomization will be of the paired communities to either experimental or control conditions. Secondary randomization of smaller social units or of individual smokers within the treatment condition can be performed to test the effect of additional levels of intervention. This "micro level" experimentation is an efficient device to expand the range of interventions to be tested beyond that of the basic design. This nesting could use either individual smokers (or only heavy smokers) or smaller social units (e.g. medical practices, neighborhoods, worksites) as the randomization units.

A collaborative trial is proposed. This approach would present a number of advantages, including pooling of data to increase power, and pooling of resources to decrease costs. The coordinative model to be used is similar to the multicenter collaborative clinical trial. A phased approach, as described below, will be used.

Phase 1. Release of a solicitation to identify and select qualified investigators and collaborating centers. Selection criteria include (1) knowledge of the communities to be studied (e.g. demographic characteristics, including SES, approximate smoking prevalence); (2) access to the community facilities required for program implementation (e.g. media, medical care system, ability to obtain in kind personnel commitments); (3) technical skills (e.g. survey research capabilities, experience in community smoking cessation programs); (4) willingness to work collaboratively (e.g. protocol development, data pooling, resource sharing).

In addition to the collaborating centers, a key group to be selected is the coordinating center. This unit will perform the central data collection and analysis, monitor quality control, and coordinate development and distribution of resources.

Collaboration by the investigators to develop a standardized protocol. The common protocol will contain the methodology to be used for the interventions and for assessment of major response variables.

At the completion of phase 1, the protocol will be presented to the Board for review and approval before commencement of phase 2.

Phase 2 will be implementation of the collaborative program.

Branch and project officers are Margaret Mattson and Thomas Glynn.

Board member Charles Cobau said he supported the concept "but I'm disturbed by the probable outcome. On the question of intensity, the greater the intensity, the greater the level of cessation. That is predictable. Is the research goal truly a scientific research goal?"

"That is not necessarily true, that the more intense (the intervention) the better," DCPC Deputy Director Joseph Cullen said. "The Minnesota program found that many not directly touched stopped smoking. The question is, in a community approach, what is the level of intensity needed to get cessation?"

Board member Lewis Kuller said, "In low income communities, where the real heavy smokers are, intensity won't help unless you change the structure of the community."

Standardized assays of biomarkers of exposure or of development of preneoplasia and early neoplasia for use in cancer control studies. Estimated number of awards, five to 10 through master agreement contracts. Estimated total cost, $500,000 for FY 1986, $1 million a year for 1987-89.

This project requests the capability to perform micronutrient, biochemical, immunologic, virologic, bacteriologic, genetic and hematologic assays for

division wide intramural and extramural activities. The project will give the division the capabilities to determine and validate the utility of these assays in new cancer prevention and control studies. In addition, the project will allow the division to augment existing activities with biomarker studies as well as to evaluate promising new biomarkers in the future.

As a resource contract, only those standardized assays available on a service basis will be sought. These assays must have demonstrated some value in terms of sensitivity, specificity or predictive value for use in this project. No work on the development of new assays will be performed through this mechanism.

These biomarkers can be divided into two broad categories. Assays that deal with chemicals or interactions of chemicals and cells are called exposure related assays. Tests that deal with detecting preneoplastic and early neoplastic conditions are called disease related assays. In terms of this classification, the major objectives of this project are:

a. Evaluation of state of art disease related assays as techniques for the early detection of cancer, which may aid in the discovery of new methods for early detection.

b. Use exposure related assays to identify high risk populations for studies in cancer detection, chemoprevention or diet intervention.

c. Use exposure and disease related assays (in addition to a cancer endpoint) to determine the efficacy of dietary and chemopreventive interventions during clinical trials, which may shorten the length of trials.

d. Use exposure related assays to assess compliance during clinical trials. For example, in exposure avoidance or protective devices clinical trials in occupational settings, exposure related assays can assess the compliance of participants in the study.

The exciting progress of basic research in molecular and viral oncology has fostered the development of new biomarkers. The emergence of biotechnology in recent years including the rapid development of monoclonal antibodies has created the opportunity for applying these biomarkers to cancer prevention and control. It is envisioned that this activity will fill the need for a division wide resource for performing biomedical assays for both intramural and extramural cancer control studies. This proposed activity would develop a systematic mechanism for the performance of assays that will be standardized, timely, efficient and cost effective. It would also provide for standardization of operation, increased quality control as well as improved coordination and management of biomarker research within the division.

The biomarkers requested for this project will include micronutrient, biochemical, immunologic, virologic, bacteriologic, genetic and hematologic disease related and exposure related assays. One classification of biomarkers is to view them as monitoring the dose of carcinogens or chemopreventive agents and their effect on early genetic/cancer responses. After exposure to an external dose of carcinogen, a certain dose is absorbed internally. The biologically effective dose can create genetic damage, followed by preneoplastic manifestations, and finally early neoplastic changes. Biomarkers have been used to measure each of these stages.

Some representative examples of biomarkers that may be used are listed below. The list is not intended to be all inclusive, but rather to represent a number of assays that could be used in cancer prevention. These biomarkers could be added to existing studies to increase the research component of the study:

Biomarkers for monitoring internal dose--fecal/urinary mutagens, selenium, vitamins A, C, E, cotinine/thiocyanate.

Biomarkers for monitoring biologically active dose--micronuclei test, sister chromatid exchange.

Biomarkers for detecting preneoplastic responses--ornithine decarboxylase, atypical breast duct epithelium, chromosomal aberration, sputum cytology.

Biomarkers for detecting early onset of cancer--quantitative nuclear fluorescence, alpha-fetoprotein, oncogene protein products.

The overall uses of the biomarkers include:

1. Monitoring the efficacy of interventions. For example, fecal mutagens could be used to monitor the effectiveness of dietary interventions.

2. Determining the relationship of the assay to the cancer endpoint. For example, does a positive quantitative nuclear fluorescence test in the cells in the urine precede the cytologic or histologic diagnosis of cancer?

3. Verifying the cessation of smoking. For example, the determination of carbon monoxide in expired air, or levels of cotinine or thycyanate in the blood may be used to verify smoking cessation.

4. Determining the degree of risk in individuals in a high risk population. For example, ornithine decarboxylase has been noted to be elevated in colonic polyps, which may be precursors of colon cancer.

5. Determining the efficacy of primary prevention methods by biological monitoring of exposed individuals. For example, the micronuclei test could be used to monitor the effectiveness of engineering controls.

6. Aiding in the early detection of cancer. For example, monoclonal antibodies may be used to quantitatively assess preneoplastic and neoplastic cell surface antigens.

7. Determining the efficacy of an assay as an early indicator of the success of an intervention. For example, the significance of a change of a positive micronuclei test to a negative result with the addition of a chemopreventive agent can be assessed.

Since it is unlikely that a single contractor can perform all these assays, a master agreement will be used to establish contracts with a group of laboratories capable of performing the desired assays. A direct benefit of the master agreement mechanism is that funding does not occur until an assay is actually required.

It is envisioned that the contractor will be responsible for shipment of the specimens to be examined from the field to the laboratory and performing the assay. In addition, the contractors will be responsible for the accrual of laboratory data, the appropriate quality control procedures as well as transferring the data to NCI.

This NCI funded resource will be made available to both intramural and extramural cancer control activities. All proposals to utilize this resource will be reviewed by and require approval of a small group (4-6) of division staff. This group will be supplemented on an ad hoc basic by NCI scientists with appropriate expertise as required. Proposals exceeding $100,000 (other than for three existing studies mentioned below) will be reviewed by the DCPC Board of Scientific Counselors Prevention Committee (staff proposal, modified--see below).

The three existing studies for which biomarker studies will be added are the asbestos clinical trial in the Occupational Clinical Network; study of high risk workers exposed to carcinogenic aromatic amines which cause bladder cancer; and the Breast Cancer Demonstration Detection Project Followup Study.

Branch and project officers are Kenneth Chu and Bill Bunnag.

Kuller argued that "there could be a tendency to add these on to studies without peer review." Upon his insistence, supported by John Ultmann and Jerome DeCosse, the proposal was amended to require review of each request by the Prevention Committee which would also be required to report those requests and disposition thereof to the full Board.

William DeWys, DCPC associate director and director of the Prevention Program, had suggested that the Board be involved only on the "big ticket items." But Kuller responded, "I would like the Board to approve everything. You could get 10 small tickets at $10,000 each, and then you would have a $100,000 big ticket."

DCPC Director Peter Greenwald said he was "not sure the Board is the best group to do scientific review." DeCosse suggested that each request be reviewed by the Prevention Committee "with consultants when necessary" and then presented to the Board. "That would save us from having to go elsewhere on the campus." The Board agreed on that approach.

Centralized source of chemopreventive agents for cancer prevention studies. One award, estimated total cost $1.7 million, three years.

Objective of this project is to establish a centralized source of agents for use in preclinical and clinical satudies by the chemoprevention program. For clinical studies, the project would provide for safe and stable storage, monitoring for stock levels and locations, inventory control to ensure timely reordering, maintenance of up to date records of shipments, and limited quality assurance capability such as shelf life. For preclinical studies, the project would receive the agents from suppliers, provide for the safe and stable storage until requested by users, repack agents to meet user needs; ship agents to users with appropriate characterization data, and handling instructions.

There are approximately 25 clinical trials involving some dozen agents and 110,000 research subjects located at 50 centers around the world. These clinical studies represent a multimillion dollar investment not only in clinical trials research but also in the cost of agents. There is also being implemented a number of preclinical studies involving in vitro screening, animal model studies and toxicology. These studies, especially the short term in vitro evaluations, will require a battery of small quantities of agents. There is also a need for information on the availability of compounds thus furthering development activities in chemoprevention. Thus, there is a need for a centralized location where agents can be obtained and a need for standardized format with regard to purchase, handling and distribution.

Thje project will develop a centralized source of agents and such services as necessary to facilitate the preclinical and clinical studies of the chemoprevention program. Upon authorization of the project officer, samples will be packaged and shipped to designated requestors. The activity will maintain a computerized system which will provide a monthly status report on shipping and receiving activity. In addition, the inventory system will provide for storage of data on chemical and physical properties, and for information on safety.

Ultmann and Cobau objected to the proposal, suggesting that DCPC should continue using the repository maintained by the Div. of Cancer Treatment. "I suggest that Peter Greenwald talk with Bruce Chabner (DCT director), and that we take advantage of DCT's drug management experience."

"We're being asked to approve the concept of having two drug stores instead of one," Cobau said. "When you set up two drug stores in the same shopping mall, you double the overhead. I think it makes more sense to have one NCI drug store."

"They serve different markets," DeCosse said. Board member Loretta Itri said that the Prevention Committee had considered duplication, "and we were informed that we had outstayed our welcome at DCT."

DeWys added, "We are second class citizens at DCT. DCT needs get first priority." Greenwald emphasized that DCT had been cooperative but "we're talking about quite different agents. The Board approved the concept, with only Robert Day opposed.

Remaining concept proposals discussed by the Board will appear next week in The Cancer Letter.

The Cancer Letter _Editor Jerry D. Boyd

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