THE CANCER LETTER
RESEARCH
EDUCATION
CONTROL

Vol. 2 No. 8

Feb. 20, 1976

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Subscription $100 per year

MORE SHAKEUPS COMING IN COOPERATIVE GROUPS; CHAIRMEN CONSIDER MULTIMEMBERSHIP PROBLEMS

One and perhaps two more cooperative groups will be phased out if the National Cancer Advisory Board accepts the recommendation of the Cancer Clinical Investigation Review Committee, the advisory body which reviews cooperative group grant applications.

CCIRC reviewed at its last meeting a number of grants up for renewal this year. *The Cancer Letter* learned that at least one will not be recommended for renewal and that one other may be on thin ice.

NCAB must approve awards cleared by CCIRC and acts as an appeal board for grants denied. The Board will consider the latest recommendations at its March 22-24 meeting.

Last fall, NCAB let stand CCIRC's decision to phase out the Western Cancer Study Group. NCI's support of that group will end July 1.

(Continued to page 2)

In Brief

KNOWLEDGE OF SURGEONS, RADIOTHERAPISTS, PATHOLOGISTS UNTAPPED, ZUBROD SUGGESTS

OVERHEARD at the annual meeting of the Assn. of Community Cancer Centers: "Surgeons, radiotherapists and pathologists know more about the natural history of many cancers than do medical oncologists. We haven't really dipped into this vast store of knowledge" – **GORDON ZUBROD**, director of the Miami Comprehensive Cancer Center. . . . "ACCC is negotiating with the NCI Div. of Cancer Control & Rehabilitation for a sole source contract to help develop the information flow on the latest types of treatment. ACCC should become a resource for getting the best treatment regimens to community centers" – **CHARLES COBAU**, Toledo Cancer Study Group. . . . "Private physicians, to participate in clinical trials, must have skilled people to collect the data. The lack of such skilled help is the major reason why the private oncologist doesn't participate in investigative efforts. Most hospitals don't know a damned thing about what to do with a tumor registry. Some way must be found to make it clinically useful" – **RICHARD OPFELL**, St. Joseph Hospital, Orange, Calif. . . . **DR. AND MRS. RONALD KOONS** of the Mountain States Tumor Institute, Boise, received the first ACCC recognition award for their "exciting, progressive" work in developing a community cancer program. . . . **FDA'S ONCOLOGIC** Drugs Advisory Committee will meet March 4 and 5, most of it in open session, in conference room G of the Parklawn Bldg., 5600 Fishers Ln., Rockville, Md. The time from 9 - 10 a.m. March 4 is set aside for public presentations, orally or in writing. From 10 a.m. - 3:30 p.m. the committee will discuss in open session NDAs on 25 drugs and once again will consider proposed guidelines for clinical testing of antineoplastic drugs. An open session also is scheduled for March 5, 9 a.m. to noon.

COOPERATIVE GROUP CHAIRMEN SEEK WAYS TO ENCOURAGE MEMBER TRANSFERS

(Continued from page 1)

More shakeups in the cooperative groups are on the horizon as they move toward implementation of multidisciplinary clinical trials with emphasis on reaching patients with early disease.

CCIRC has reviewed supplemental grant applications for funds to finance converting to multimodality studies. At the time of review, the NCI appropriation for the current fiscal year was still a question mark, and the amount to be made available for the supplemental awards undetermined. DCT Director Vincent DeVita said that it would be at least $2 million, which would be transferred from the division's contract program.

DeVita said that was to be considered a floor, not a ceiling. Previous discussions with CCIRC and with cooperative group chairmen indicated NCI might put as much as $5 million into the supplemental awards.

Not all groups will get the supplemental awards. Simon Kramer, chairman of the Radiation Therapy Oncology Group, denounced at a group chairmen's meeting the decision by CCIRC to deny his application for supplemental funds.

"Our group was not reviewed on its merits," Kramer charged. "A prior decision had been made that we weren't to be multidisciplinary. It seems you have arbitrarily decided that only those groups originally specializing in chemotherapy shall be multimodal. It's an absurdity, with no justification."

When DeVita pointed out that three of the chairmen at the meeting were radiotherapists and one was a surgeon, Kramer demanded, "Do you deny such a decision has been made?"

CCIRC Chairman Giulio D'Angio, who is also chairman of the Wilm's Tumor Study Group, responded that "the general tendency was to go by past track records. RTOG was not looked upon as a multidisciplinary group."

"If you deny us the funds to operate as a multimodality group, that is a self-fulfilling prophecy," Kramer said. "By preventing us from bringing in others, you are creating a Catch-22 situation."

D'Angio told Kramer, "You are appealing a review decision. It is inappropriate to do so here." Barth Hoogstraten, acting chairman of the chairmen's committee, agreed, "This is not the place to bring up the merit of the review."

DeVita suggested that the difficulty might be in defining RTOG's mission. "Is it to take part in clinical trials as a radiotherapy group? Or is it to look at specific problems in radiotherapy? Frankly, the way I look at it is that the reason for RTOG's existence is to make sure that all the latest and best refinements are being used. There is a reason for the group, but not to be another multimodality group. RTOG is a unique, specialty group."

D'Angio insisted that the CCIRC review was based on merit and not on a predetermined policy that would exclude RTOG.

Another problem which DeVita referred to as "very difficult . . . sticky . . . no one wants to deal with it" is that of multiple membership of an institution in several cooperative groups. "There are some institutions with memberships in five or six cooperative groups," DeVita said.

Problems this situation leads to include competition for resources within the institution—patients, staff, beds, other facilities; the splitting up of various specialists among several groups—radiotherapist in one, pediatrician in another, which will impede multimodality studies.

NCI hopes the problem can be alleviated by encouraging reorganization, making it possible for people to move to another group by facilitating grant transfers, assuring that grants won't be lost or reduced.

NCI is counting on the centers to take the lead, but the long history of some of the relationships will make this difficult. "It will take a very strong center director to make those changes," one NCI executive said.

The American Assn. of Cancer Institutes recently considered the impact of multiple funding mechanisms upon center initiated clinical research. It was the consensus of AACI's Task 10 committee (which deals with clinical research) that the variety of funding sources has a centrifugal effect on the cohesiveness of clinical investigations within a center and interfered with the ability of the center to develop its leadership role in clinical research.

NCI Director Frank Rauscher told the AACI committee that NCI's policy is that coordination of clinical research is a matter for the center, not NCI.

AACI committee members had a number of comments:

—The centers are far more than a passive receiver of funds. They have a leadership role in clinical research; diversity of funding can be destructive to science and good medicine at the cneter. Discretionary funds for clinical research would help the centers in their leadership role.

—Cooperative groups and centers have different capabilities and should have equal access to funding to carry out their missions. At the present time only the cooperative groups are funded.

—Most of the innovative advances in therapy have come from full time investigators at the large centers. With interinstitutional protocols of the cooperative groups the large number of participants dilutes the influence of the investigators at the centers, so that centers play only a minor role in cooperative group research.

—The situation today is far different from that of 15-20 years ago. Previously there were few centers, and cooperative groups were needed. Today, with

many centers, the need for cooperative groups is much reduced.

—With a number of centers and their access to community hospitals in their region, there is an opportunity for interdisciplinary studies of early cancer. It would serve today's needs much more to have centers join forces for particular studies, rather than continue large scale support of the cooperative groups which have dealt almost exclusively with advanced disease.

There were a number of suggestions from NCI staff as to how to meet the problem:

—When any center participated in more than one cooperative group, the various grants could be combined under a single group.

—A supplement might be given to the center core grant for discretionary use in center initiated clinical research.

—Cooperative groups could be prevented from using their increased funds to proselytize the resources of the center (as has occured in several instances).

Other comments included:

—NCI will have limited ability to start new grants this year and next, and it may be impossible to alter the present system.

—Money is not sole driving force in clinical research.

—Cooperative groups have ignored the centers and the centers have held aloof from cooperative groups. Now they are coming together and NCI must be aware of this transition phase and its resulting dilemmas.

The cooperative group chairmen agreed unanimously that NCI should take steps to support transfers and asked the staff to prepare a statement of policy for consideration at the next chairmen's meeting.

The following discussion on this issue involved DeVita, D'Angio, Hoogstraten, Eastern Cooperative Oncology Group Chairman Paul Carbone, Northwestern Cancer Center Director Nathaniel Berlin, Southeastern Cancer Study Group Chairman John Durant, and Primary Breast Cancer Therapy Group Chairman Bernard Fisher (comments are not verbatim and have been edited to confine the report to the issue of transfers):

Carbone: I'm looking for new members, who can help us become multimodal, and we will get rid of some who cannot.

DeVita: That will include the transfer of members?

Carbone: Yes.

D'Angio: Any transfer must be acceptable to both sides, and then it must go through review.

Berlin: What are the steps required for transfers?

D'Angio: One, it must be mutally acceptable, especially to the receiving institution. Two, the principal investigator should be agreeable. Three, submit it to NCI staff. Four, it will then go to CCIRC for review.

Hoogstraten: Since the transfer will be with funds, will this be looked upon as an opportunity to review the institution? If so, it will hamper transfers.

Durant: Some people transferring may have larger grants. Will they be consolidated under a single PI? Will he lose control over his funds? How will you handle that?

D'Angio: We will approve the transfer at the current level of funding. The transfer must be mutally acceptable, to the receiving group, to the group he is leaving, and of course to the PI.

Berlin: What's the incentive if he has to lay his grant on the line?

D'Angio: If he's strong, he shouldn't have to worry.

DeVita: But that's a key point. If the intent is to reorganize, and he has performed reasonably well, we should say, come on over. We have to be somewhat protective, to encourage the move.

D'Angio: The intent of the review is to strengthen the group, and to protect the chairman.

Hoogstraten: Those are good intentions. But you shouldn't do it. They won't transfer. We should make it as easy as possible. The review should be for organization only, not for review of funding.

D'Angio: There have been a number of requests for transfer from the group being dissolved.

DeVita: A large number of requests. The purpose of looking at a transfer should not be considered a threat to his funds, but only to get a handle on what is going on.

Carbone: This review clearly should look at the individual member. Is it possible for individual members to be encouraged to transfer from a group that is folding? We can get some good members, if we can transfer his grant.

D'Angio: That is possible, if the group chairman is responsive and continues his level of funding.

DeVita: You lost me. The Western grant terminates July 1. If an individual transfers, he has to come in under the new group's grant.

D'Angio: I meant we should encourage him to transfer prior to folding the other group.

Durant: A good member might be available from the folding group.

Fisher: He's a free agent.

Durant: Like a ballplayer, available to the highest bidder.

DeVita: This won't work if you go out and start raiding other institutions. A no risk transfer mechanism will sort this out.

Berlin: Could a principal investigator transferring lose his principal investigatorship?

DeVita: Yes. That's an institutional decision.

Carbone: You could make him co-principal investigator.

DeVita: Let's discuss the role of center directors. How does a cooperative group deal with the center? He may feel a group chairman is taking part of his team away.

Carbone: We've got to meet with them, get cooper-

ative groups and centers together. All benefit. They feed each other. The problem exists when the cooperative group is located outside the center.

Durant: Groups in centers can help each other, particularly with control activities. We have a synergistic relationship. We discuss responses to RFPs when we see it would compete with group activities, and we discuss grant applications if it could interfere with existing activities (Durant is also director of the Univ. of Alabama Comprehensive Cancer Center).

Carbone: There will be conflict when a center develops a protocol that competes with the groups.

D'Angio: As a center director (Univ. of Pennsylvania-Fox Chase Comprehensive Cancer Center), I have on my executive committee principal investigators of cooperative groups. They can't ignore each other.

Berlin: Most of the centers want to do their clinical research through the cooperative groups. Large scale cooperative studies will be with patients in the centers.

DeVita: Whatever works will be used. We all have one goal, to cure cancer. Some institutions have strong clinical research of their own, some with cooperative groups.

NCI REPORTS $120 MILLION – 17% OF BUDGET – FOR ENV. CARCINOGENESIS

A comment heard frequently from critics of the Cancer Program has been something like this:

"Environmental factors cause 85% of all cancer, so how come NCI spends only 10% (or 5% or 2%) of its budget on environmental carcinogenesis studies?"

Until recently, NCI could offer only some broad estimates of how much it spends on environmental carcinogenesis in answer to that question. No one had any hard data until NCI staff came up with some figures for the President's Cancer Panel which indicates that 17.5% of the budget goes into such research, directly and indirectly.

Those figures show that NCI spends $120 million on environmental carcinogenesis, out of a total budget of $687 million (those figures were based on the President's budget of $687 million for the current fiscal year; with the veto override, NCI will get $762 million, and probably result in a corresponding increase for environmental carcinogenesis. If it does not, then the percentage would be somewhat less than the 17.5%).

"Those figures do include some for construction, training, and management," Director Frank Rauscher told the Panel. "They are pro-rated from the entire budget. If you pin it down to actual operations, it would not be this much. But it is not fair to exclude those items, because they always compare what we're spending for environmental carcinogenesis to the total budget, which of course includes all the overhead."

According to that rationale, NCI spent $100.2 million in the area in fiscal 1974, and $117.9 million in 1975. The estimate for 1977 fiscal year, which starts Oct. 1, is $122 million, but again that was based on the President's budget and likely will be increased considerably.

The breakdown by NCI divisions in the 1977 budget shows $43.2 million in Research Resources & Centers; $62.2 million in Cause & Prevention; $1.5 million in Biology & Diagnosis; $3.6 million in Control & Rehabilitation; and $11.5 million for construction, management and other overhead.

Cause & Prevention, which includes the Carcinogenesis Program, is where most of the action is. The Carcinogenesis Program itself (which does not include viral oncology), is budgeted for $43.1 million; co-carcinogenesis (viral-chemical), $2.4 million; field studies & statistics, $8.6 million; smoking & health, $6.1 million; and diet & nutrition, $2 million (a figure certain to be increased).

Carcinogenesis Program Director Umberto Saffiotti told the Panel that of his $43.1 million, $20 million could be considered strictly for environmental carcinogenesis.

Traditional research grants currently are funded at $7.6 million, included in the Research Resources & Centers budget estimate of $42 million for the 1976 fiscal year. They are broken down as follows:

+ Molecular structure-activity relationships, identification and synthesis of carcinogens/metabolites, development of analytical procedures (environmental specimens), $.9 million.

+ Biochemical changes in physiological compounds and processes produced by chemical carcinogens, effects of chemical carcinogens on cell structure, ultrastructure and function, $1.4 million.

+ Properties of cells transformed by chemical carcinogens, development of carcinogen screening procedures, biological models, bioassay systems, $.5 million.

+ Carcinogenicity screen, definitive evaluation, $.2 million.

+ Metabolism of chemical carcinogens, identification of proximate and ultimate carcinogenic forms, carcinogenicity-mutagenicity relationships, DNA damage by chemical carcinogens, DNA repair, $3.6 million.

+ Factors which initiate, promote, or inhibit the action of chemical carcinogens, $1 million.

Norbert Page, chief of NCI's Carcinogen Bioassay & Program Resources Branch, presented a summary of the bioassay operations and of major findings in 1975:

"The primary goal of the bioassay operations segment is the identification and evaluation of chemical carcinogens, particularly those of environmental and occupational significance.This goal is pursued through the bioassay of these chemicals, either singly or in combination, in long-term animal studies. At the same time, the bioassay operations segment is

attempting to improve the sensitivity and reproducibility of present bioassay systems as well as to develop new ones.

"After a chemical is selected for bioassay a number of sequential activities are undertaken.These include (1) evaluation of all known safety data and other relevant information to determine testing priority; (2) procurement, chemical analysis, and work-up of special procedures; (3) assignment to a bioassay laboratory; (4) pre-chronic toxicity testing; (5) long-term bioassay and pathology evaluation of its effects; (6) analysis and evaluation of the data; and (7) preparation of a technical report. A large amount of advance planning is necessary to ensure the successful and efficient accomplishment of each stage. Resources are needed to provide analytical capability, animals, and data management. Coordination of these resources is needed to ensure that high quality animals of a specified age are available at the proper time and in sufficient quantities, that the bioassay laboratory has adequate manpower to effectively conduct each phase of the study, and that the data are collected and made available in a timely manner. During the performance of the bioassay the progress and results are continuously monitored. If the results indicate that the chemical may be a potential human health hazard, the Dept. of Health, Education & Welfare and the relevant regulatory agencies are notified.

"The actual bioassay consists of a pre-chronic and a chronic phase. During the former, the maximum tolerated dose of the chemical that can be given in the chronic phase is predicted. The chronic phase must be carefully planned to assure that the proper experimental design is used and that the bioassay is conducted under optimal conditions. Particular attention must be given to ensure the safe handling and disposal of the test chemical and waste materials. Data are provided to the Carcinogenesis Bioassay Data System (CBDS) on the experimental design, clinical and survival observations, and pathology diagnoses. Analysis of the data can be made at any time during the study. After all the data have been appropriately analyzed and evaluated, they are published in scientific journals and/or as part of a comprehensive technical report.

"Because of the insufficient staff manpower available for the management of the bioassay program it was decided to establish a prime contract which would provide the necessary management effort under the scientific direction of this segment's staff.

"After an extensive competitive evaluation, the bioassay prime contract was awarded in March, 1974 to Tracor-Jitco Inc. The Tracor-Jitco staff has relieved the members of the bioassay program of much of their immediate contract-related administrative and management duties. As a result, the NCI staff has had more time to concentrate on the scientific needs of the program.

"Although the bioassay prime contractor has direct control over many of the bioassay laboratories, NCI still retains ultimate responsibility for all of the program's activities. The bioassay program staff members are kept aware of the activities of the prime contractor through daily communication, reports, and frequent progress meetings.

"At the start of the fiscal year the bioassay operations segment was directly responsible for 12 contracts, one of which has terminated. The prime contractor had an additional four projects that were acquired as subcontracts in FY 1974. During the current fiscal year the prime contractor has acquired another six subcontracts which have been transferred from direct NCI management. Thus, the transition of these efforts has resulted in the prime contractor becoming responsible for a total of 10 subcontracts and the bioassay operations segment retaining control of five contracts.

"The bioassay operations segment also provides support for and monitors the large-scale bioassay project at the NCI Frederick Cancer Research Center. During the fiscal year the segment provided partial funding for pathology support and for data management contracts, both of which are administered by the information and resources segment.

"During the fiscal year approximately 540 chemicals were in one or another stage of the testing program. Of these 112 were pharmaceutical products, 82 industrial chemicals, 94 pesticides and agricultural chemicals, 36 metallic compounds, 31 natural plant products, and 9 food additives. Most of the remainder have multiple uses or are structural analogs tested for structure-activity relationships. Approximately 225,000 animals have been used during the fiscal year. These include about 105,000 rats of the Osborne-Mendel, Fischer/344, and Sprague-Dawley strains; 105,000 mice of the Swiss, C57BL/6 and hybrid B6C3F1 strains; and 15,000 hamsters and other species.

"The bioassay of each chemical for carcinogenicity requires a substantial commitment in time and money. Three years or longer may be needed to complete each bioassay at a cost of $100,000 or more. Thus, every effort must be made to ensure that each chemical nominated for bioassay is thoroughly evaluated before resources are committed to it. A Chemical Selection Working Group (CSWG) has been established to carry out this critical evaluation. The CSWG is chaired jointly by Elizabeth Weisburger, chief, Carcinogen Metabolism & Toxicology Branch, NCI, and Carl Wessel, bioassay prime contract project director. Nomination of chemicals for consideration by the CSWG are received from NCI staff, from other federal agencies, from information contracts, and from the scientific and technical community. For each chemical, the CSWG endeavors to gather as much information as is practically possible, including a summary of the experimental studies reported in the open literature regarding its toxicity, information

on its occurrence, production, use, and human exposure, as well as data on its physical and chemical properties, structural relationship to known carcinogens, metabolism, and epidemiological observations. A summary of this dossier is prepared along with the CSWG's recommendation and submitted to the associate director for carcinogenesis who has the ultimate responsibility of determining which chemicals are selected for bioassay. Plans are being developed to form a chemical selection committee. Its members will be from NCI staff and the chairman will be Umberto Saffiotti, associate director for carcinogenesis; ad hoc outside expert consultants will be used. In the 18 months that the CSWG has been in existence, approximately 1,100 chemicals have been considered, of which about 110 have been recommended for bioassay.

"A major activity during this past year has been the review of existing carcinogenesis testing methodologies and the preparation of detailed NCI *Guidelines for Carcinogen Bioassay in Small Rodents.* These guidelines have been implemented in routine carcinogenesis tests conducted by the bioassay operations segment.

"One of the most important aspects of the bioassay program is the collection, analysis, and reporting of data. The data from studies initiated within the last 2½ years have been entered into the computerized Carcinogenesis Bioassay Data System (CBDS). Data from earlier studies have been collected and stored in progress reports and other formal documents. The CBDS collects, monitors, and stores bioassay data. The system has been designed for the complete or selective recall of these data. In addition, the CBDS contains chemical and bioassay sub-systems that provide information on each chemical under test or projected for study as well as other data related to them. During the year, emphasis was placed on refining the data input to CBDS and developing a capability for the routine generation of data tables. The data entry, SNOP-coding, and similar functions are done under contract to EG&G/Mason Research Institute.

"The need for a competent and thorough evaluation of the bioassay data is self-evident. However, since neither the bioassay program nor many of the contractors have the capability to analyze data, the assistance of biostatisticians from outside of the program has been sought. The primary source of help has come from the statisticians associated with the Field Studies & Statistics Program.

"Although bioassay contractors are encouraged to submit their testing results to scientific journals, it is necessary that the data be properly tabulated and evaluated prior to their publication. For this reason, all bioassay data must be reviewed and approved by NCI prior to their release. However, because of their voluminous nature, publication of all the data collected from a bioassay study is not possible. Therefore, the scientific community rarely has the opportunity to review the bioassay data in their entirety. As a result, the preparation of a technical report series has been undertaken to provide complete documentation of each bioassay study. A technical report will be prepared on each chemical tested and will contain complete information, from the rationale for its bioassay through an interpretation of the test data.

"The major resources needed to conduct a carcinogen bioassay study are (1) analytical chemistry, (2) animal production, (3) testing laboratories, and (4) data management. The bioassay program's analytical chemistry resource is located at the Midwest Research Institute. Midwest Research Institute, a subcontractor to the prime contractor, is responsible for characterizing the test chemicals as well as determining their proper mixing and handling procedures. The Frederick Cancer Research Center is the primary source of animals used in the bioassay program. The mice and rat colonies at FCRC are periodically restarted with breeders obtained from the NIH Div. of Research Services. The testing laboratories must meet certain minimum standards before they qualify to participate in the bioassay program. Foremost among them are their ability to safely handle the test agents and provide the needed capability to ensure long-term animal survival. The Carcinogenesis Bioassay Data System (CBDS) is the bioassay program's main data resource. CBDS is operated under contract by EG&G/Mason Research Institute. The main function of the CBDS is to collect, selectively retrieve, and report data collected in the bioassay program. Besides these major resources, close collaboration has been developed and maintained with other members of the carcinogenesis program's staff.

"The increase in number of chemicals placed on test in the FY 72-73 period is now realized by large workloads in pathology evaluation, data analysis, and preparation of reports. As the technical report series is still in the developmental stage, contractor scientists have continued to report their test results by the usual methods; i.e., scientific journals, conferences, progress reports, etc.

"Some major findings obtained by projects of the bioassay operations segment during the 1975 fiscal year:

"The studies at the Univ. of Cincinnati, designed to investigate cocarcinogenesis of u.v. light and a variety of industrial chemicals, are nearing completion. A major finding is that n-paraffins enhance the rate of the appearance and number of tumors in mice exposed to u.v. light at 254nm and 290-320nm. Also, mice developed tumors after topical applications of n-dodecane and n-tetradecane and exposure to a "non-carcinogenic" wavelength of greater than 350 nm u.v. light.

"The native population of the Island of Curacao in the Caribbean exhibits an unusually high incidence of esophageal cancers. It has been suggested that these

these may be related to the use of herbaceous folk remedies. At Howard Univ. a number of these herbs are being fractionated and screened for carcinogenicity by subcutaneous administration to rats. For those herbs that have been found to contain carcinogenic materials, the activity was mainly associated with the tannin-containing fractions.

"A variety of alkylating agents used in the chemical industry were tested for carcinogenicity as New York Univ. Medical Center. Several of the agents were found to be carcinogenic in mice. Studies have been conducted by various routes of administration and demonstrate that the route of exposure can often influence the outcome of the test.

"At the Univ. of San Francisco a large number of metals and their compounds have been studied. Although most were screened by intramuscular injection in rats, some were also administered by the oral route. Both nickle and cadmium were found to produce local fibrosarcomas after i.m. injection. Other metals tested produced questionable positive results or failed to show any carcinogenicity.

"A project at Temple Univ. has established experimental methods for investigating the effects of changes in the effective thickness of stratospheric ozone on UV photo carcinogenesis.

"The mice and rats being used to study the carcinogenicity of five chemicals at the Dow Chemical Co. will be sacrificed early next fiscal year. After the tissues are examined and the data evaluated, a technical report will be prepared on each chemical.

"At Gulf South Research Institute 20 pesticides are being tested for carcinogenic activity. An important finding has been that for many of the organochlorine compounds an initial dose level of about 25 percent of that which appeared to be the maximum tolerated level, based on six-week prechronic studies, would have more closely approximated the true MTD for the length of the chronic phase. Several of these pesticides appear to be carcinogenic and are now undergoing detailed evaluation.

"A total of 43 environmental chemicals are under investigation for carcinogenicity at Hazleton Laboratories. Inhalation studies have been initiated on two halogenated aliphatic compounds (ethylene dibromide and dibromochloropropane) which were reported last year to be highly carcinogenic when given orally to both mice and rats. For a number of other chemicals, evidence of carcinogenicity is developing; these are now in different stages of evaluation.

"Carcinogenicity studies are underway on a number of dibenzodioxins at the IIT Research Institute. Many of these highly stable environmental contaminants are extremely toxic and tend to accumulate in the food chain. Prochronic toxicology has been completed for tetra- and hexa-chlorodibenzodioxins and their chronic study is now being planned.

"Forty-two chemicals are under test at Litton Bionetics; 19 of them have completed the treatment period in mice and 12 of them in rats. The necropsy findings indicate that several of the compounds appear to be carcinogenic in one or both species; the tissues from these animals are now being evaluated.

"Fifty-four chemicals or combinations of chemicals are being evaluated in mice and rats for carcinogenic potential at the Mason Research Institute. Histopathological examination is now in progress on the animals treated with the first series of 12 chemicals and on some of the animals in the second series of 20 agents. The remaining chemicals have either entered the chronic test phase or their toxicities are being studied.

"The Midwest Research Institute continues to serve as the bioassay program's analytical chemical resource. Specific tasks include chemical identity, assay, and stability analyses; formulation of mixing protocols, and feed and dosed-feed analyses. A large variety of techniques are used in the different analyses that are done.

"A comparative study of six inbred strains of rats is being concluded at the Papanicolaou Cancer Research Institute. These strains include the Fischer line 344, A x C line 9935 Irish, August line 990, Marshall line 520, S x F line 40814, and Zimmerman line 61. With the carcinogen N-OH-N-2-fluorenylacetamide, the most frequent site of tumors was in the liver. The next most frequent tumor type was squamous cell carcinomas of the stomach. About 35% of these tumors were found in the August line 990 rats. Nearly half of the control rats are still alive.

"At the Southern Research Institute a number of chemotherapeutic drugs and related chemicals are being tested for carcinogenicity. Each chemical is administered by a route comparable to human exposure. Procarbazine induced tumors of the nervous system in both mice and rats. A high incidence of reticulum cell sarcoma was found in mice treated with isophosphamide. Other chemicals that have been tested have also demonstrated varying degrees of carcinogenic potential.

"The study designed to investigate the combined effects of chemical carcinogens and other chemicals is nearing completion at the Stanford Research Institute. The last group of animals will be sacrificed early next fiscal year. After all the histopathology is completed and the data collected and collated, they will be submitted for special analysis under a separate contract at the Univ. of California Medical Center, San Francisco.

FORD APPARENTLY PASSES UP RECISION, NEW MONEY TO START FLOWING MARCH 1

More than $7 million withheld from new NCI grantees since last fall will start flowing to them by mid-March if, as now seems probable, President Ford decides against submitting to Congress a new recision request for the HEW budget.

The override of Ford's appropriations bill veto and a decision not to invoke the recision process will make available more than $40 million to NCI grantees from fiscal 1976 funds. All of that amount will be for new grants and for approved renewals which otherwise would not have been funded.

NCI will get $74 million more than the President had requested. The extra money will permit more adequate funding of new programs, such as Diet & Nutrition and supplemental awards to the cooperative groups.

The White House Office of Management & Budget has not yet officially announced there would be no recision. But word filtered down to NIH from HEW headquarters last week that the President had decided to give up the struggle and release the money. OMB by law must start release funds 30 days after they are appropriated; in this case, that was the day the Senate voted to override the veto, Jan. 28.

NCI intends to obligate its entire appropriation of $762 million by June 30, although that no longer is the cutoff date for the fiscal year and funds could be carried through to Sept. 30, the new FY termination date. That amount was appropriated for the original 12 months, with a prorated extra amount for the three month, so-called "wedge period."

NCI now is sweating out whether or not OMB will permit it to go ahead and fill the 79 additional positions ordered by Congress. The conference report on the appropriations bill decreed that NCI's position ceiling would be lifted from its present level of 1,889 to 1,968. In the past, OMB has frequently chosen to ignore language in committee reports accompanying legislation although courts have held that such reports clarify the intent of Congress. NCI executives feel the additional positions are absolutely essential to effective management of the Cancer Program.

The process now starts all over again. Director Frank Rauscher is scheduled to appear before Chairman Daniel Flood's House HEW Appropriations Subcommittee Feb. 25 in hearings on the 1977 fiscal year budget.

The President asked for $687 million for NCI in 1977, a totally unrealistic figure now that the 1976 appropriation has been established at $762 million.

DIET, NUTRITION PROGRAM TO FUND PROJECTS WITH PROGRAM GRANTS

NCI's Diet, Nutrition & Cancer Program has added a third funding mechanism to its repertoir, the program grant, in addition to contracts and cancer research emphasis grants (CREG). DNCP thus will be the first segment of the Div. of Cancer Cause & Prevention to make use of a mechanism other than contracts and CREGS.

DNCP Director Gio Gori said that RFAs (request for applications) for the grants will be issued within two weeks. Applicants will have from one to two months to write up their proposals. Review will be done by two new committees to be established to review DNCP grant and contract proposals. The grant awards will be sumbitted to the National Cancer Advisory Board for its approval at the Board's Sept. 12 meeting, permitting awards to be made prior to Sept. 30 with 1976 fiscal year funds.

Although DNCP had seemed at the outset an ideal program for CREG, Gori discovered CREG review, using the NIH Div. of Research Grants study sections, would require a minimum of 14 months. That would not permit funding with the current year appropriation, so Gori had determined to use contract exclusively this year while channeling some projects into CREG for 1977 funding.

NCI Director Frank Rauscher, who long has felt that all program divisions should have access to the grant mechanism, decided there is no reason why DNCP should not have that tool without the time consuming process of going through NIH. Rauscher and Gori feel that the roles of diet and nutrition are so new to the cancer field that a major share of the program's money had to be set aside for investigator-initiated research. The grant mechanism is the best way to handle that, although Gori had said the contract RFPs would be written so broadly and would permit so much investigator freedom that they in effect would be grants.

Gori said, "The way it looks now, we'll split about 50-50 between grants and contracts, although that could change." Contract RFPs will be issued for projects when the work scope can be specified in detail. Grants will be used where the experimental approach is best left to the inventiveness of the investigator, although the mission and objective still will be specified.

Gori believes the use of grants, in addition to CREG, may spill over to other programs in Cause & Prevention, and perhaps to other divisions as well. In fact, the Div. of Cancer Control & Rehabilitation already has awarded grants other than CREG, and the Div. of Cancer Treatment funds the Clinical Cooperative Groups with grants.

Until DCT took over the cooperative groups and Cancer Control initiated its grants program, all NCI grants were channeled through the Div. of Research Resources & Centers, with review by NIH study sections.

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Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.