THE CANCER LETTER
RESEARCH
EDUCATION
CONTROL

Vol. 1 No. 48

Nov. 28, 1975

The Cancer Letter, Inc.

Subscription $100 per year

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

FDA ONCOLOGIC DRUG COMMITTEE AGREES THAT "KITTY FIGHT" WITH NCI SHOULD BE NEGOTIATED

The flap between NCI and the Food & Drug Administration over delays in approving INDs and FDA's proposed guidelines for clinical tests of anticancer drugs is a "kitty fight" that should be resolved immediately by negotiations between the two agencies.

That was the opinion of Michael Shimkin, chairman of FDA's Oncologic Drugs Advisory Committee, former NCI executive and member of various NCI advisory groups, professor of community medicine and oncology at the Univ. of California (San Diego), and past president of the American Assn. for Cancer Research.

All those credentials should lend plenty of weight to Shimkin's opinions, and he has seldom been reluctant to express them, usually in definite terms. But whether even Shimkin's forceful persuasion can move the FDA bureaucracy remains to be seen.

"Such fights are counterproductive," Shimkin said when the Onco-

(Continued to page 2)

In Brief

NCI TELLS COOPERATIVE GROUPS TO SUBMIT APPLICATIONS FOR EXTRA MULTIMODALITY FUNDS

COOPERATIVE GROUPS have been advised by NCI's Div. of Cancer Treatment to submit supplemental grant applications as soon as possible, to fund expansion into multimodality studies. "We recognize that not every group is suitable for a multimodality program," said DCT Director Vincent DeVita. DCT hasn't promised any definite sum, but the figure of $10 million has been mentioned as the amount NCI may be willing to add to the $22-24 million going to the cooperative groups in the current fiscal year. . . . **HOUSE-SENATE** conferees met last week again, trying to decide what to do about the controversial antibusing amendment to the HEW appropriations bill. They didn't get anywhere, won't meet again now before next week, with Congress having taken off the entire Thanksgiving week. The amount decided upon for cancer is firm, at $743.5 million, plus about $22 million to be approved later for training programs. The delay leaves HEW appropriations on about the same schedule as last year, when President Ford signed the bill in mid-December, held up release of funds until mid-January and then submitted a recision request. By the time that was disposed of, NCI was into the final quarter of the fiscal year and had to hustle to get all funds obligated. NCI executives expect the same situation this time, except that with the change of the fiscal year from July 1 to Oct. 1, starting next year, they'll have three extra months to get NCI appropriations spent. Those extra months come during the traditional vacation time, however, so it probably won't be any easier on NCI staff. Also, the delays will only add further confusion to grantees and contractors who never can be sure of when they'll get their money.

SHIMKIN COMMITTEE AGREES WITH NCI POSITION ON PHASE I GUIDELINES

(Continued from page 1)

logic Drugs Advisory Committee met at FDA last week. "The worst thing we can do is to write more and more guidelines and create conflict with each other. This committee should recommend that FDA swallow its pride, get together with NCI, and write guidelines agreeable to both."

The difficulties between the two agencies arose a few weeks ago when FDA refused to approve investigational new drug applications submitted by NCI, Sloan-Kettering and M.D. Anderson (***The Cancer Letter***, Nov. 14).

FDA officials admitted the refusals were based on technical variations from regulations rather than on the quality of the submissions, an admission that infuriated the drug sponsors, NCI executives and investigators who had been planning clinical trials with the drugs.

Another serious difficulty arose when FDA released its proposed guidelines for testing anticancer drugs. Some members of the Div. of Cancer Treatment Board of Scientific Counselors objected to the automatic, and minimum, 30-day delay between submission of an IND application and its approval. "Why can't we just send it in and start using it?" asked one. "We know what we're doing at least as well as anyone at FDA. These drugs have gone through very extensive preclinical studies before they reach that stage, and they have had NCI review and institutional peer review. How many patients will die during those 30 days who might have been helped by the drug?"

The most serious complaint about the guidelines was expressed by DCT Director Vincent DeVita. He objected to the implication in the proposed guidelines that no therapeutic intent be considered in phase I studies. "I'll never put a drug into a patient without any intention of helping him," DeVita said, indicating that NCI would strenuously oppose that section of the guidelines.

Shimkin's committee supported DeVita's position. Committee member Philip Schein, Georgetown Univ., acknowledged that phase I studies basically are to determine human toxicity. "Actually, it is something else. No physician puts a drug into a patient not looking for therapeutic intent," Schein said. "This has to be placed into perspective. Actually we are looking for clinical activity. Hopefully we are using drugs with the intent of finding clinical activity. When we use drugs on any patient, we assume they will have a therapeutic effect. . . Those phase I guidelines won't hold up."

Julian Ambrus, Roswell Park, agreed. "We never run an honest phase I trial. We always expect therapeutic activity. I would be a great deal happier if we don't separate phase I and II, and run them simultaneously."

Charles Moertel, Mayo, pointed out that the entry of advanced cancer patient into experimental programs "is the best possible thing for them. I remember very well when those patients were kept in the back of wards, physicians would not see them, or they would be sent home, with no work on relief of pain. Physicians were discouraged because there was little that could be done for them. This (entry of patients into clinical studies) is treatment, damn good treatment. Yes, the patient is in an experiment, and yes, he is getting the best possible treatment."

Margaret Sullivan, M.D. Anderson, led the discussion on the section of the guidelines dealing with testing of pediatric drugs.

"One principle in drug testing is that trials should be conducted in the population in which the drug will be used," Sullivan said. But certain cancers occur only in children, and the guidelines require that initial testing of a new drug be done in adults. In fact, initial testing for toxicity of drugs intended solely for pediatric cancer generally is done on normal adult volunteers.

Sullivan said that children usually are much more tolerant of drugs than are adults, and that there is a wide safety margin in extrapolating adult data to children.

Moertel suggested that "we are painting ourselves into a box on this one. In a rapidly fatal situation, why wait for adult tests? Since children generally tolerate drugs better anyway, why not proceed immediately with them?"

Sullivan agreed that this might be considered provided proper and thorough informed consent is obtained from parents or guardians.

FDA HOLDS UP NDA ON BCNU, BUT NCI WILL PROCEED WITH NEW DRUG SEMINAR

If the disputes between NCI and FDA over the IND delays and the guidelines do not provide enough ammunition to feed the "kitty fight," still another hassle has surfaced.

DCT had scheduled another of its new drug seminars for mid-December in Washington on the assumption that FDA would have approved the new drug application (NDA) for BCNU and CCNU, two of the nitrosoura group of antitumor agents developed by DCT. NCI had contracted with Bristol Laboratories to work up the NDA, and Bristol will have an exclusive license to market the drug when the NDA is approved.

As generally happens when FDA undertakes review of the NDA, time schedules are rarely met. The NDA for BCNU and CCNU has not been approved. FDA will not offer any estimate of when it will be approved ("If I told you, it would greatly affect Bristol stock," Robert Young, FDA's group leader for oncologic drugs told ***The Cancer Letter***). However, ***The Cancer Letter*** learned that approval might not come before mid-1976.

NCI plans to go ahead with the new drug seminar anyway. It will be held Dec. 15-16 in the Washington Hilton Hotel, starting at 9 a.m. Dec. 15 and 8:30 a.m. Dec. 16. The drugs have been extensively tested in trials under the IND procedure, have been particularly effective on brain tumors, and have been tested against acute leukemia, large bowel cancer and lung cancer. Results of those trials will be discussed by investigators.

FDA'S CONTROVERSIAL CLINICAL TEST GUIDELINES FOR ONCOLOGIC DRUGS

The preamble to FDA's proposed guidelines for clinical investigation of antineoplastic drugs was published last week in ***The Cancer Letter.*** The complete guidelines appear below.

FDA officials emphasized that these are still in the formative stage and are seeking comment from interested persons. Send suggestions to FDA, Bureau of Drugs, 5600 Fishers Lane, Rockville, Md. 20852.

PHASE I STUDIES

I. Objectives

A. Tolerance. These studies should define an agent's non-therapeutic effects such as limiting toxicities, their degree of reversibility, dose-response relationships, time courses, etc. Therapeutic schedules should be sought which will maintain the patient at maximally tolerated doses for a period of time sufficient to allow recognizable neoplastic regression, according to the natural history of a subject's particular cancer.

B. Pharmacology. For those agents administered orally, absorption and bioavailability profiles should be determined. Rates of drug clearance from the plasma, biotransformation, and excretion should be established, and estimates of tissue distribution and concentration, and therapeutic dose-response relationships, time courses, etc., if feasible, should be obtained.

II. Population of Interest/Sample

Phase I experimental subjects are traditionally patients with histologically proven malignant disease, which at the time of the study is no longer amenable to conventional form(s) of therapy (which must be specified in advance). To be meaningful, tolerance studies must be carried out in relatively stable subjects who will probably survive a required minimum period of observation. Investigators must be certain and prepared to document that "carry-over" effects of antecedent therapies have been dissipated, and that they can recognize and separate the effects of the investigational drug from concurrently administered drugs and the disease itself. Since the primary goal of phase I studies is not a determination of therapeutic effect, experimental subjects need not have objectively measurable tumors.

III. Controls

Since phase I studies are primarily observational (naturalistic) in character, historical controls which must be prospectively defined are generally appropriate.

IV. Experimental Maneuver

Initial drug doses should be well below the level at which pharmacological or toxic effects might be expected. As a rule of thumb, an initial drug dose in man for cytotoxic agents is usually one tenth of the highest non-toxic dose or the minimum toxic dose in the most sensitive animal species on a mg/kg basis or 1/3 the LTD in mg/M2 (with weight measurements on the ideal or actual level which ever is less.)

Dose increases should be made in increments most appropriate to the slope of the animal toxicity curves. The dose should be judiciously increased until a dose is found which produces clear signs of a therapeutic or major non therapeutic effect.

Effects of the drug, both therapeutic and non-therapeutic, are determined and validated by serial histories, physical examinations, and laboratory determinations. The latter should include general profile tests, and appropriate specific tests as suggested by preclinical findings. A careful search should be made for organ specific toxicities such as CNS, cardiac or pulmonary toxicities which may not be predicted from the preclinical studies.

Because no therapeutic benefit may accrue to the experimental subject, nor need such benefit be sought, and yet the subject may suffer serious nontherapeutic consequences, the patient must be fully informed of the "experimental" nature of the study, i.e., the generally large degree of therapeutic uncertainty and his consent must be free of constraint i.e., the patient must be free to participate or refuse. If by participating in the study, the subject will incur an additional financial obligation, he should be so informed explicitly.

PHASE II STUDIES

I. Objectives

A. Therapeutic effect. These studies should unambiguously specify which types of tumors respond and do not respond to the experimental agent being studied. Dose-response relationships, time courses, etc. should also be defined concurrently.

B. Non-therapeutic effects. By careful documentation of non-therapeutic effects, and their dose-response relationship, time courses, etc., an assessment is made as to whether these effects are tolerable in the context of the achieved therapeutic effect.

II. Population of Interest

Any subject with a malignant tumor is a potential candidate for study. Tumor types should generally be assigned a priority for testing commensurate with their potential responsiveness as suggested by preclinical or phase I studies. The disease state to be examined must be fully and carefully described in terms of all relevant prognostic (risk) factors that affect the natural history of the disease in question. For example, specification of the following factors may be necessary: age, clinical extent of the disease, rate of progression of the tumor, response to previous therapy, state of nutrition, functional status of the subject, etc.

III. Sample

Patients with histologically proven malignant disease, which at the time of the study is no longer amenable to its conventional form(s) of therapy (which must be specified in advance), are candidates for study if and only if they also have objectively measurable malignant disease. Spatial measurements are preferred, but in some cases only temporal measurements will be available. To be meaningful phase II studies must be carried out in relatively stable subjects who will probably survive a required minimum period of observation. Investigators must be certain, and document that carry over effects of antecedent therapies had been dissipated, and that they recognized and separated the effects of the experimental drug from concurrently administered drugs and the disease itself.

IV. Controls

Since there is no conventional therapy to which the investigational drug's effect(s) can be compared, and since malignant disease is almost uniformly fatal, historical controls can be used, so long as the investigator can clearly specify beforehand the natural history of the disease (quantitatively and qualitatively) of the experimental subject(s) when untreated. Having so specified a reference group, the investigator can analyze his data appropriately.

As those subjects with spatially measurable disease will have had their disease quantitatively characterized before treatment, each subject can also serve as his own control with respect to his measurable disease (after treatment).

V. Experimental Maneuver

The response variables (therapeutic and non-therapeutic) along with the methods by which they will be measured must be specified. A therapeutic index (a scale of clinically meaningful results) must be presented; for example, length of survival, 25% reduction in the sum or a 50% reduction in the product of the two largest diameters taken at right angles to each other of a lesion, maintained at least 30 days with no evidence of progressive disease elsewhere, etc. An endpoint (failure) must also be defined.

Until a therapeutic failure is declared, or a meaningful therapeutic effect is documented, the patient should be treated at maximally tolerated doses (schedules) as suggested by preclinical data, available clinical data, and the disease under study. Observations must be made over a period of time sufficient to allow all events of interest to occur(generally

to the death of the patient).

Because no therapeutic benefit may accrue to the experimental subject, and at times there may be no substantial reason to believe any will, and yet the subject may suffer serious non-therapeutic consequences, the patient must be fully informed of the "experimental" nature of the study, and his consent must be free of constraint.

VI. Analysis

Although a statistical analysis is not specifically required, this type of analysis is presently most widely applicable. The primary comparison to be made is between the experimental group and the historical control group. The hypothesis (null) generally tested is that the experimental agent has no effect on the response variable size of the tumor rate of progression of disease, length of survival, lekopenia, GI distress, etc.), ($H: \mu a - \mu b = 0$).

The appropriateness of the chosen statistical model must be justified in terms of the experimental material and underlying assumptions. The level of significance and power of the test statistic must be specified in advance. Statistical significance is not a goal or end in itself, but only a guide in interpreting the data.

PHASE III STUDIES

I. Objectives

A. Therapeutic effectiveness. Substantial evidence is gathered to show that a drug administered, in a defined manner, is an effective (clinically meaningful) treatment for a particular neoplasm. In general, to be approved, the agent must be shown to be either superior to a standard therapy; or no different than a standard therapy, and thereby possibly be an alternative therapy; of clinical benefit to a substantial proportion of patients, or of clinical benefit to a well defined group (any size) of patients.

B. Non-therapeutic effect. Substantial evidence is gathered to show that the non-therapeutic effects are tolerable (relative safety) in the context of the achieved therapeutic effect.

II. Population of Interest

Tumors shown to be response in phase II studies. The disease state to be treated must be unambiguously described in terms of significant prognostic characteristics (risk factors). Appropriate demographic and personal characteristics should also be included in defining the population. In short, the population must be well defined.

III. Sampling

An adequate and representative sample must be obtained. Entry criteria and the method by which a valid sample is to be gathered and each subject characterized must be described. The most appropriate subjects are usually previously untreated, newly diagnosed cases. Well conducted, cooperative trials are suggested when no investigator alone can recruit a sufficient number of subjects over a reasonable period of time.

IV. Controls

Phase III trials must be controlled. The usual control group is one on "standard therapy" (active treatment) but historical controls may be appropriate. The method by which the sample is to be divided must be presented, and efforts must be made to avoid bias when assigning subjects to the various groups. This is usually accomplished by random assignment of subjects to the various groups.

V. Therapeutic Maneuver

The treatment program must be soundly based on prior experience and findings. It must be carried out over a sufficient length of time to allow all events of interest to occur (usually the reamining lifetime of the patient). The response variable, methods of measurement, a therapeutic index, and an endpoint must be defined. The most meaningful response variable and that of primary interest is the length of survival of the subjects. This should not be an absolute goal in itself, however, and an honest attempt to assess the quality of life must also be made. Other response variables might be the rate of progression of disease, length of remissions, etc.

The method by which instruments and their operators are to be calibrated, and their quality, reliability and precision established maintained, and assured must be presented. The method by which observations are to be faithfully recorded and bias eliminated or minimized must be described.

The use of innovative experimental designs which minimize the exposure of subjects to the treatment thought to be inferior (such as "play the winner") is encouraged. Crossover of therapeutic failures to the "other" therapy may be of use.

VI. Plan of Analysis

Specification, in advance, of the procedure by which the data is to be analyzed insures that meaningful analysis will be possible. Although a statistical analysis is not specifically required, this type of analysis is presently the most widely applicable. The appropriateness of the chosen statistical model must be justified in terms of the experimental material and the underlying assumptions. The level of significance and power of the test statistic must be specified in advance. The comparison to be made is between the experimental group and the active treatment (standard therapy) group or historical control groups. The primary response variable of interest is survival time. Other response variables might be proportion of responders, rate of progression of disease, frequency of each non-therapeutic effect, length of remissions, etc.

The definition of the risks involved with the use of a therapeutic agent must necessarily be an abiding concern. Additionally, relative safety in terms of benefit and risk can only be established in the context of efficacy.

PHASE IV AND BEYOND

The test of the hypothesis that a combination of agents is superior to single agents or other combinations should be conducted after it has been demonstrated that each member of the combination is clinically active (effective) alone, or when there is clear and convincing preclinical evidence that each member of the combination will materially contribute to the desired therapeutic effect. The design, otherwise, should be that of a phase III study. It is assumed that the effect of any one agent in the combination is confounded in the effect of the combination.

Since a drug's development is a continuing process, each physician who uses an agent has a responsibility and obligation that goes beyond the patient he is treating. By carefully characterizing his patient's disease, and making and recording his observations accurately, he may observe new, clinically significant therapeutic and non-therapeutic effects which he should bring to the attention of the medical community. Progress in the treatment of cancer with drugs will be facilitated if each practitioner is enlisted, in a meaningful way, as an investigator.

PLAN OF DEVELOPMENT

An efficient, well-ordered plan of development of a drug is highly recommended. The sponsor is responsible for coordinating and monitoring the research efforts of participating investigators in such a way that the conclusion that an agent is effective or ineffective, safe or unsafe is reached with the exposure of as few subjects as is possible or practical. Once substantial evidence has been gathered that an investigational new drug, administered in a defined manner is safe and effective, the sponsor has an urgent obligation to prepare his data, and submit an NDA (New Drug Application).

PEDIATRIC CONSIDERATIONS

In the effort to make new drugs available quickly for general use, care should be taken not to neglect patients in the pediatric age group. Too often, the information needed to administer agents properly to this group is not obtained during the initial phase of drug development, and these patients essentially end up as "therapeutic orphans." To avoid this situation, the following overall guidelines are suggested:

1. The initial testing of an investigational new drug should be done in adults.

2. Phase I tests in children should be based upon and begun as soon as valid, adult phase I data becomes available.

3. Phase I tests in children should be completed during the phase II tests in adults, i.e. before phase III tests in adults commence.

4. Phase II tests in children should be in progress, or a reasonable plan of phase II testing in children must be prepared, before the actual approval of the NDA. If the disease in question occurs in adults and children, initial phase II tests in adults are suggested.

UCLA, NYU, OHIO STATE COMPREHENSIVE STATUS DELAYED, PERHAPS TO SPRING

UCLA, New York Univ. and Ohio State will have to wait a while longer before NCI officially confers comprehensive status on their cancer centers.

The National Cancer Advisory Board in a closed session last week heard presentations on the status of the three applications from the Board's Subcommittee on Centers and from Simeon Cantril, chief of the NCI Centers Program. ***The Cancer Letter*** learned that all three centers were still lacking in some of the requirements established for comprehensive designation, in the Board's opinion.

The Board recommended to NCI Director Frank Rauscher that approval be delayed until the deficiencies can be pointed out to the centers and remedies effected.

The dealy probably means that no more comprehensive centers will be added to the 17 existing ones this year, and that such action will not occur prior to the next NCAB meeting, in March.

One effect of the delay will be to take some pressure off Rauscher. The White House has told NCI that the maximum number of comprehensive centers should be no more than 20, although the National Cancer Act gives the power to make that determination only to the NCI director. Once UCLA, NYU and Ohio State join the list, Rauscher might have to ignore a Presidential order to add any more—and there are 23 other institutions which have told NCI they are seeking comprehensive status.

With three designations, or "identifications" as NCI prefers to call it, being made next year, Rauscher could hold off on any others until after the 1976 election, with the possibility that a new Administration might be more flexible. It's possible that none of the others will be ready before then, anyway.

CONTRACT PLANNED TO ENCOURAGE HEALTH INSURERS TO REIMBURSE FOR SCREENING

What will happen to NCI-supported cancer control programs when the demonstrations are completed, lessons learned (hopefully), organizational structures established—and federal dollars cease to flow?

That's the tough question the Cancer Control & Rehabilitation Advisory Committee turned over earlier this year to a reimbursement working group headed by Grace Monaco, a Washington attorney and member of the advisory committee.

Monaco's group reported to the committee recently that the prime example it can use in helping Div. of Cancer Control & Rehabilitation contractors and grantees become self supporting when federal funding ends is in the category of screening and detection. And the problem to overcome there is the fact that few health insurers include reimbursement for screening and detection in their plans.

The group has decided to develop a contract proposal, to be offered to Blue Cross/Blue Shield on a sole source basis, to design a prototype reimbursement program for screening and detection. BC/BS is a non-profit health insurance organization, and Monaco's group suggested that DCCR consider developing similar contracts with a private health insurance company and with a health maintenance organization, but probably not until after the BC/BS has been implemented.

A contract with the private firm in all probability would involve a competitive RFP, and possibly so would the HMO contract.

"The objective of the potential RFP flows from the fact that screening and early detection offer the most effective means of reducing cancer mortality in selected cancers, but these programs are not now generally included in the basic health insurance packages," Monaco reported to the advisory committee.

BC/BS probably will be required under the contract to develop an administrative package including guidelines for the program target areas, standards of facilities, target population, an education package both professional and public to inform providers and the insured of the availability of the screening program as a basic health insurance benefit.

BC/BS has indicated it would emphasize screening services in non-hospital settings, including physicians' offices, clinics, group practice facilities, neighborhood health centers, mobile units, even schools, industrial sites and business offices.

"They have shown a keen awareness of the importance of the data collection and evaluation of any program of this nature and suggest that their data will be collected in proparation of economic evaluation of cancer detection procedures in a manner which will permit cost/benefit comparisons of alternative screening screening procedures, premium costs, and prospective national health insurance programs," Monaco said. "They will consider medical treatment costs and work-time costs in determining the real costs of a detection program."

CONTRACT AWARDS

Title: Population-based cancer epidemiology research center
Contractor: Univ. of Iowa, $470,469.

Title: Studies of herpesvirus antigens and virions in neoplastic cells
Contractor: Johns Hopkins Univ., $88,000.

Title: Studies on isolation and characterization of Type C virus and diagnostic testing and service functions
Contractor: Microbiological Associates, $65,082.

Title: Viral-chemical carcinogenesis studies
Contractor: Microbiological Associates, $66,667.

Title: Establish and maintain a blood serum bank
Contractor: Mayo Foundation, $105,000.

Title: Support services for studies on the application of animal virus model systems to neoplasia
Contractor: Litton Bionetics, $493,000.

Title: Collection, processing and distribution of animal specimens
Contractor: Litton Bionetics, $170,000.

Title: Fibrinolysis as a parameter of in vitro
Contractor: Children's Hospital of Los Angeles, $85,958.

Title: Fecal flora studies
Contractor: UCLA, $447,314.

Title: Support services for studies of spontaneous and virus induced neoplastic formation
Contractor: Meloy Laboratories, $104,160.

Title: Support studies for immunological and biochemical studies of mammalian viral oncology
Contractor: Meloy Laboratories, $72,499.

Title: Immunotherapy of disseminated human cancer
Contractor: M.D. Anderson, $409,000.

Title: Macrophage activation in tumor immunity and immunotherapy of rat mammary tumor
Contractor: Robert B. Brigham Hospital, Boston, $109,300.

Title: Rhesus monkey histocompatibility studies
Contractor: Litton Bionetics, $215,887.

Title: Chemical characterization of purified thymic products of other agents promoting lymphocyte differentiation
Contractor: Yale Univ., $65,118.

Title: Immunotherapy: Development of animal models for evaluation of therapy with neuraminidase treated tumor cells
Contractor: Yale Univ., $55,000.

Title: Biochemistry and diagnostic use of human tumor antigens
Contractor: Yale Univ., $39,960.

Title: Cancer Immunotherapy: Animal models for treatment of minimal residual systemic tumor
Contractor: Pennsylvania State Univ., $138,032.

Title: Spontaneous and virus induced neoplastic transformation studies
Contractor: Meloy Laboratories, $170,015.

Title: Administrative support services for the Div. of Cancer Biology & Diagnosis
Contractor: Kappa Systems, Arlington, Va., $28,690 and $311,107 (two contracts).

Title: Preparation of Carcinogens compounds
Contractors: IIT Research Institute, and Southern Research Institute, under basic ordering agreement.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for information purposes only. RFPs are not available.

Title: Support services to maintain studies of spontaneous and virus induced neoplastic transformation
Contractor: Meloy Laboratories, Inc.

Title: Spontaneous and virus induced neoplastic transformation studies
Contractor: Meloy Laboratories.

Title: Chemical carcinogen-induced noduligenesis and tumorigenesis in mouse mammary gland organ culture
Contractor: Univ. of Nebraska.

Title: Studies of molecular events leading to transformation by RNA oncogenic viruses
Contractor: Litton Bionetics.

Title: Demonstration of tumor specific transplantation antigens in animals and human tumors with the microcytotoxity assay
Contractor: Fred Hutchinson Cancer Research Center

ROSEMOND CALLS FOR BAN ON HIGH TAR, NICOTINE CIGARETTES, CITES PROGRESS

George Rosemond, outgoing president of the American Cancer Society, urged a ban on all "high tar and nicotine cigarettes," and called for nationwide public support for the government's suit against the six largest cigarette manufacturers "for violating an agreement to give adequate display to the health warning on cigarette advertising."

In his presidential address at the annual ACS meeting, Rosemond issued a challenge to "those newspapers and magazines who take cigarette advertising for very understandable reasons." Rosemond asked whether their editors will show the courage and fortitude that has made the free press one of the proudest institutions of our country, and "give their editorial support to a request that the warning message in the cigarette ads should, at the very least, be as conspicuous as the message urging young and old to inhale carcinogens."

The Federal Trade Commission has asked the Justice Dept. to seek civil penalties against the six companies for violating a 1972 order. The suit alleges that the health warnings were not large or prominent enough.

Following the 1971 ban on TV and radio advertising of cigarettes, the cigarette companies switched more than $200 million to newspaper, magazine, billboard, posters and promotional advertising signs. ACS leaders have charged that the cigarette companies deliberately underplayed the health warnings.

Rosemond noted that Sweden has officially announced its commitment "to a smokeless society" and that England has banned any advertising which

depicts smoking as being pleasurable in any way and that France is planning to do the same. He also called for cessation of federal tobacco subsidies and for diverting the money to antismoking advertising campaigns.

Briefly surveying some of the progress made in cancer research, Rosemond cited:

- Isolation of a virus from the laboratory grown cells of a patient with acute myelogenous leukemia, which may open doors to further advances in virology.
- Development of preliminary evidence that immunotherapy may be of value in systemic treatment of patients with melanoma.
- A drug combination that has shown a promise of effectiveness in the treatment of advanced colon cancer.
- The first evidence that some forms of advanced non-Hodgkins lymphoma can be controlled for extended periods by chemotherapy.
- Encouraging results with L-PAM as well as three-drug combinations in patients with advanced breast cancer.
- Anticancer drugs have dramatically improved survival of young patients with osteogenic sarcoma.

Describing some of the cancer control activities of the society, Rosemond emphasized the "good results to date in our five-year campaign to get every woman in America to have a Pap test." He said that special efforts were being made to reach rural communities as well as non-English speaking and low education groups. He added, "We know that through the Pap test, early stages of cancer can be identified five to 10 years before any symptoms appear."

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NO1-CP-65752-69

Title: *The biology of neoplastic liver lesions in mice*
Deadline: *Jan. 17*

The Bioassay Operations Segment of NCI's Carcinogenesis Program is interested in developing a contract effort to study the biology of neoplastic liver lesions in mice. The mouse is one of the most commonly used animals in carcinogenesis research, including long-term carcinogen bioassay. Although liver neoplasms are frequently encountered in this species, additional research on these proliferative lesions is needed to better characterize and define their biological nature. The use of current experimental techniques should result in a clearer understanding of the evolution of these neoplastic lesions and the development of criteria by which they can be more precisely classified. Since the mouse is one of the primary species used by the Bioassay Operations Segment to screen environmental chemicals for carcinogenicity, every effort must be made to define the nature and relevance of the proliferative liver lesions found in this species.

As more than one contract may be awarded, offerors may apply for part or all of the work described in the below section.

The contractor will perform studies to evaluate the biological characteristics of both spontaneous and induced liver tumors in mice. Biochemical, immunological, morphological, transplantation or other appropriate techniques may be used. The study should also attempt to determine the reversibility of the early lesions and to establish as clearly as possible their preneoplastic or neoplastic nature.

Strains of mice with both low and high spontaneous liver tumor incidences will be compared. In defining the "spontaneous" liver tumors, consideration should be given to their possible induction by environmental contaminants; e.g., those found in feed, water, and air.

A comparative study of the mouse liver lesions, induced by at least two different chemicals, will be made. Chemicals to be used will include one which is known to induce mouse liver tumors but has a negative or marginal effect at other organ sites and in other species. Another test chemical will be one known to induce unequivocal liver cancer in the mouse as well as in at least one other species. The most suitable test chemicals are those that produce minimal toxic effects at organ sites other than the liver. For comparative purposes, it is also desirable to use one dose level of each chemical which will induce liver tumors only after long and about equal exposure periods.

The number of animals used and the treatment regimens should be adequate to perform the necessary determinations. The final pathological examination will be done in accordance with NCI bioassay pathology procedures.

Offerors should have a demonstrated competence in chemical carcinogenesis. Also, a familiarity with the problem, prior studies of mouse liver tumors, and the state of relevant knowledge should be displayed. The rationale and appropriate data to support the selection of the mouse strains and chemicals to be used should also be presented.

It is expected that a doctoral level person, or one with equivalent experience, with working knowledge in chemical carcinogenesis research will act as project leader. The government anticipates that the proposed contract will span a three year performance period.
Contract Specialist: Linda Waring
Cause & Prevention
301-496-6361

The following competitive RFPs are scheduled to be issued by the Div. of Cancer Control & Rehabilitation during fiscal year 1976. The RFPs will be available in December or early January. Deadlines for proposals will be determined at that time.

RFP NO1-CN-65338-05

Title: *Structured programs of continuing care (the "Hospice" concept)*

This will provide for a demonstration of the "Hospice" concept for the terminally ill cancer patient. This concept emphasizes primarily the quality of survival rather than the length of survival for advanced cancer patients. Such demonstration must provide for an at-home program as well as a non-hospital in-patient facility.
Contract Specialist: Shelby Buford
Control & Rehabilitation
301-427-7984

RFP NO1-CN-65339-09

Title: *An information clearing house on services and facilities available for rehabilitation of cancer patients*

This will provide for a compendium listing resources that are specifically attuned to, and providing rehabilitation for cancer patients. The information to be collected will include new prosthetic devices, new techniques and approaches and facilities specially designed to aid in the rehabilitation of cancer patients.
Contract Specialist: Earl Klevins
Control & Rehabilitation
301-427-7984

RFP NO1-CN-65340-05

Title: *Development and implementation of at-home rehabilitation programs*

There is still a need to demonstrate that the in-patient rehabilitation traditionally provided to the cancer patient can, with a more creative approach, be provided to the cancer patient within one's home. An increasing number of cancer patients are denied the benefit of follow-up rehabilitation after definitive treatment because they are unable to return to the treating facility for rehabilitation. With innovation, much of what is needed can be provided within the patient's own home, utilizing the patient's family members in the rehabilitation process.
Contract Specialist: Shelby Buford
Control & Rehabilitation
301-427-7984

RFP NO1-CN-65333-05

Title: *Training programs for maxillofacial prosthodontists*

The increasing incidence of head and neck cancer and the long survival rates being achieved with adjunctive therapy demand that the dental specialist needed for oral facial restoration be more readily available. This RFP will be directed to those who can train prosthodontists for the sophisticated maxillofacial restoration currently needed for head and neck cancer patients.
Contract Specialist: Shelby Buford
Control & Rehabilitation
301-427-7984

RFP NO1-CN-65334-05

Title: *The development, application and evaluation of cancer prescreening methodologies*

This RFP will be issued seeking a group of contractors who, through a cooperative network, will develop, apply, and evaluate multi-site cancer prescreening instruments (questionnaires) and other program components designed to differentiate from the general population those individuals at high risk of having or developing cancer. This program will encompass the entire spectrum of activity beginning with the definition of subpopulations at high risk of cancer and proceed through selective screening of high-risk individuals and close surveillance and follow-up of program participants.
Contract Specialist: Helen Tissian
Control & Rehabilitation
301-427-7984

RFP NO1-CN-65335-25

Title: *Screening for malignant and premalignant lesions of the uterine corpus*

This will be issued seeking one to three contractors who will undertake the design, implementation and thorough evaluation of modalities for the detection-diagnosis of premalignant and malignant lesions of the uterine corpus. Emphasis will be placed on comparative and definitive evaluation of those modalities potentially useful for outpatient screening of high-risk populations.
Contract Specialist: Helen Tissian
Control & Rehabilitation
301-427-7984

The Cancer Letter—*Editor* JERRY D. BOYD

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