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NCI PROPOSES THREE NEW GRANT PROGRAMS IN NUTRITION AND RESEARCH; DRCCA BOARD, NCAB APPROVAL REQUIRED

Three new grant programs in nutrition education and research development were proposed last week to the National Cancer Advisory Board, which took no formal action on them but indicated support. Two of the programs will require concept approval from the Div. of

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In Brief

TRANSITION TEAM DENIES IT IS SEEKING NEW NCI DIRECTOR; GARB UNDERGOES SURGERY AT M.D.A.

REAGAN TRANSITION team has denied that a search has been launched for candidates to replace Vincent DeVita as NCI director. At least one cancer center executive has been contacted by someone claiming to be a member of the transition team, asking for names of people who could be considered for the job. "I don't know of any such effort," transition team member David Winston told ***The Cancer Letter.*** His responsibilities include NIH and the Public Health Service. "The rumors flying around now are unbelievable." . . . **SOLOMON GARB**, who as chairman of the Citizen's Committee for the Conquest of Cancer and a member of the Senate Panel of Consultants was a key figure in development of the National Cancer Act of 1971, underwent surgery for stomach cancer last week at M.D. Anderson. Surgeons found no evidence of metastasis, but the pathology had not been completed by press time this week. Mail may be sent to him, c/o M.D. Anderson Hospital, 6723 Bertner, Houston, Texas 77030. . . . **MARVIN RICH**, executive VP and scientific director of the Michigan Cancer Foundation, has been elected chairman of the board of directors of the Ohio Valley-Lake Erie Assn. of Cancer Centers. Other officers of the largest regional association of cancer centers in the U.S. are Charles Cobau, director of the Toledo Clinic, president; William Dugan, director of clinical oncology at Methodist Hospital in Indianapolis, vice president; and David Yohn, director of the Ohio State Univ. Comprehensive Cancer Center, secretary treasurer. . . . **SHELDON SAMUELS**, member of the National Cancer Advisory Board, reported that the investigation of Frederick Cancer Research Center by the Board subcommittee he headed "was a can opening operation, and behold—there were no worms." FCRC employees include a "skilled body of scientists, well coordinated. . . who have demonstrated excellence. No matter what happens to the contract (with Litton Bionetics for the operation of the center), that body of scientists will be protected. Dr. (Harold) Amos and others on earlier boards did their work well and got started on the right path (Amos chaired Board subcommittees which made various recommendations for FCRC)."

CLINICAL EDUCATION SUPPLEMENTS, NEW RESEARCH, PLANNING GRANTS PROPOSED

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Resources, Centers & Community Activities Board of Scientific Counselors before they can be implemented.

The new programs are:

• Supplements to clinical cancer education grants to stimulate education of physicians in nutrition as it relates to cancer treatment and prevention. Those eligible to compete for up to 10 awards would be the institutions with clinical cancer education grants, now numbering 64. The supplements would be up to $40,000 each for two years and could be used for a wide variety of items, including adding additional trainees, faculty development, curriculum development, and materials. "It would be left to the investigators to come up with ideas," said Margaret Edwards, chief of the Clinical Manpower Branch.

The proposal will be submitted to the DRCCA Board at its meeting in January for concept approval, unless Edwards is able to obtain that approval by mail from Board members before then. She is anxious to get the program started and to get applications in by the March 1 deadline, for review and award with 1981 fiscal year funds.

• Nutrition research training. This would consist of four or five grants totaling $400-500,000 a year, with each grantee institution training about seven cancer scientist-nutritionists. Grants would be funded through the NRSA T-32 mechanism, with applications to be solicited either through an RFA or program announcement. Barney Lepovetsky, chief of the Research Manpower Branch, said he will submit the proposal to the DRCCA Board in January. Regular NRSA deadlines would apply, with the first awards to be submitted to the NCAB at its October meeting for FY 1982 funding.

• Planning grants. Diane Fink, who heads the Diet, Nutrition & Cancer Program, told the NCAB that these grants would be aimed at building interdisciplinary relationships between nutritionists and oncologists. They would offer investigators the opportunity to start pilot nutrition and cancer research projects. They would be two year awards, with the amount variable but no more than $100,000 each. After two years, the investigators would have to compete for support through the traditional (R01) or program project (P01) mechanisms.

The planning grant proposal does not yet fall under the jurisdiction of DRCCA, although NCI Director Vincent DeVita said the entire DNCP will be moved from his office to DRCCA in the near future. Fink said she would proceed with the grants only with NCAB approval, but members indicated they needed more time.

NCAB Chairman Henry Pitot appointed an ad hoc subcommittee which will meet before the Board's next meeting, to consider the proposal. The members are Bruce Ames, Harold Amos, Maureen Henderson, Irving Selikoff, Philippe Shubick, and Gerald Wogan.

Fink and other staff members gave NCAB members an overview of nutrition related research carried out or supported throughout NCI. William DeWys discussed nutrition activities of the Div. of Cancer Treatment; Andrew Chiarodo review nutrition research in the Organ Site Programs; Elizabeth Anderson described the research in the Div. of Cancer Biology & Diagnosis; Appasaheb Patel reviewed that in the Div. of Cancer Cause & Prevention; and Regina Ziegler discussed the saccharin case control study conducted by the Field Studies & Statistics Program of DCCP.

The saccharin study found that the sweetener, "if it is a carcinogen at all, is a very weak one," Ziegler said.

"We are badly in need of some good hypotheses," Selikoff said. "The human animal is extremely variable. We should be careful about drawing conclusions in nutrition studies. I can hardly remember what I ate a week ago, let alone 20 years ago. We need prospective studies.

"My own feeling is, I love to see the cancer maps (developed by FSS on county by county cancer incidence in the U.S.)," Selikoff continued. "I like the colors. But when you look at the numbers, you get the impression the colors differ more than the numbers. County rates are notoriously unstable. Maps don't tell us much about in and out migration, where people were 30 or 40 years ago."

Shubick said he agreed that saccharin was not a carcinogen, although "there are some complex minimal effects. The general conclusion is that there are no carcinogenic effects in large numbers. . . but we should continue to look at some small groups."

"We all agree that at best, saccharin is a very weak carcinogen," DeVita said. "What bothers me is that large doses then (referring to consumption 10-20 years ago by the study subjects) are small doses now. Many children drink five cans of diet soda a day."

"Maybe 15 years from now we will find an increasing incidence of bladder cancer among those children," Selikoff said. "The conclusion that saccharin is not a carcinogen or is only a weak one is based only on those studies. . . . But we did not begin to use saccharin in large amounts until the 1960s. Bladder cancer deaths looked at (in the FSS study) occurred only 12 years after that pattern of use started. If saccharin had affected the incidence at all, it would be a very powerful carcinogen. Even benzyne doesn't show [its carcinogenic effects] for 30 years. We shouldn't establish a policy based on data that are not there."

BRMP WORKSHOPS PLANNED; DCT BOARD BALKS AT SIZE OF INTRAMURAL BUDGET

Four more workshops have been planned by the Biological Response Modifier Program subcommittee of the Div. of Cancer Treatment Board of Scientific Counselors, starting with one Dec. 10-12 on the role of NK, ADCC and macrophages in tumor rejection and as indicators of BRM activity.

Others are Feb. 23-25 on potentiality of cloned antibody in cancer therapy; March 2-4 on potential utilization of lymphokines in cancer therapeutics; and June 1-3 on potential role of T-cell subpopulations and their modulation in therapy of tumor.

Each of the workshops will be held in Bethesda and each will be published by Raven Press as part of the initial series of publications aimed at stimulating development of the Biological Response Modifer Program.

Workshops have already been held on augmenting agents and on growth and maturation factors. Enrico Mihich, chairman of the subcommittee, presented a summation of the augmenting agents workshop at the meeting of the Board of Scientific Counselors last month. Excerpts from that summation follow:

This conference on augmenting agents had as its objectives: 1) the identification of new agents for the BRM program, 2) an assessment of their readiness for clinical development and 3) an assignment of priorities for clinical development.

The first objective was accomplished. Detailed reports were provided on fractionation of BCG and C. parvum as well as the current status of other natural products such as nocardia rubra cell wall skeletons, microbial polysaccharides and staph phage lysate. There were equally detailed reports on a variety of interferon inducers, synthetic polymers and miscellaneous agents which could not be otherwise categorized on the basis of their source, structure or mechanism of action.

The second objective was the assessment of the readiness of these materials for clinical development. The criteria for this include such factors as the availability of a uniform product, toxicity data suggesting reasonable safety, evidence that a biologic response of consequence in cancer control is modified, identification of a method for establishing the optimum dose, schedule and route of administration in man and demonstration of a significant antitumor effect in animal models.

Some of the inconsistent results with BCG immunotherapy trials which led many investigators to doubt its clinical utility can be traced to the multitude of preparations employed. These BCG preparations varied widely in strain characteristics, the number of viable organisms per dose, and the quantity of debris. It is not surprising that the biological effects of these preparations also varied widely. The consistent availability of a uniform product is an essential prerequisite for the conduct of clinical studies.

Toxicity data are routinely gathered prior to the clinical application of any therapeutic agent. However, special consideration must be given to unusual problems which may be posed by these new categories of agents.

When administered via the customary percutaneous routes, the first generation of augmenting agents (the microbial agents) generally failed to modify the biological responses under surveillance, although in the few instances where it was measured, they did so on intravenous administration. Improved application of first generation agents, availability of newer materials and improved monitoring techniques have led to demonstrable modification of biological responses. The question that remains is whether or not these responses are important in the control of tumor growth. For example, Dr. Herberman presented a considerable quantity of data indiciating that a variety of biological response modifiers influence NK cell activity. What is the in vivo significance of this observation? With transplantable animal tumors there is a correlation with survival for those tumors which are sensitive to NK cells in vitro. There are no data on primary autochthonous tumors in animals and man. Do alterations of macrophage number and/or function influence tumor growth? The data suggest that the answer is yes but additional research is required. At present, we must focus on biological responses of only putative clinical significance.

In the early clinical trials of immune augmenting agents, dose, route and schedule of administration were most often arbitrarily selected. Failure to demonstrate a therapeutic benefit and differences in results between trials were frequently attributed to variations in these parameters. The clear demonstration in animal models that immune modulation and control of tumor growth are both dose dependent makes careful phase 1 studies a necessity. But how can optimum dose, schedule and route to determined? Toxicity may not be dose-limiting with many of these materials. Further, the maximum tolerated dose may not be the optimum immune augmenting dose. Therefore, identification of optimum dose will likely be linked to the optimum modification of a biological response. Of necessity this biological response must be one that is correlated with antitumor effect in animals and is also measurable in man.

Because of these present limitations in our ability to quantitatively assess clinical readiness, the agent selection process will be in some part empirical at the outset. As selected agents undergo systematic clinical development, the knowledge gained will enlighten our empiricism and make the selection process more rational.

With a general view toward these criteria, but focusing on antitumor effect, what is the current

state of preparedness for clinical development of the various materials discussed? The first day of the workshop was devoted to natural products and their subcomponents. This seems appropriate as these materials dominated clinical trials for the greater part of the 70s. The use of BCG or any other living microorganism has certain obvious disadvantages. Further, it has been repeatedly speculated that by using fractions of the microbial adjuvants, therapeutic efficacy would be maintained or increased and toxicity would be reduced. Dr. Ribi described a portion of his extensive experience with BCG fractionation. Indeed 300 ugm of BCG cell walls attached to oil and suspended in saline is as effective intralesionally in the guinea pig-hepatoma model as a 6 x 10^6 viable organism (31/53 vs 30/51 cures respectively). Further, fractionation approaches will likely allow the eventual separation of toxic and therapeutic effects, the dissection of mechanisms of action and a broadening of routes of administration. However, there were no data indicating a therapeutic superiority over whole living BCG in an animal model. In man, Dr. Vosika demonstrated tumor regression with intralesional administration of cell wall skeleton (CWS, M. smegmatis) /P3/oil with a series of 17 melanoma patients. The magnitude and frequency of response seem similar to that reported by others with living BCG.

Dr. Tuttle described his experience with mechanical and chemical fractionation of C. parvum. Again these procedures will likely allow separation of toxic from therapeutic effects and allow a dissection of the mechanism of action. The sensitivity of certain fraction functions to suppression by oxidation with sodium periodate and regeneration by reduction with sodium borohydrate is exciting. Pyridine extraction yields a fraction, 300 ugm of which in combination with muramyl dipeptide and P3 is as effective as 10,000 ug of whole cells. However, relative efficacy on a weight basis aside, the magnitude of the therapeutic effect of whole cells has not been significantly improved upon.

The therapeutic efficacy of equal amounts (300 ugs) of nocardia rubra and BCG CWS was compared in a variety of animal models. On an equal dose basis N. rubra CWS seemed therapeutically superior. For example, it produced 6/13 cures in the spontaneous mammary adenocarcinoma model versus only 2/17 with BCG CWS. However, full dose response curves are required to determine if there is a real difference between the two materials. A clinical trial is currently in progress in which patients with stages 1 through 4 lung cancer are randomized after primary treatment to no further therapy or N. rubra CWS. At present there are 60 patients on the control arms with a median survival of nine months compared with 54 treated patients with a median survival of 15 months. Although this difference is significant ($p = 0.03$), its magnitude is modest and questions remain regarding the comparability of treatment and control groups. These factors coupled with a lack of efficacy in the guinea pig-hepatoma model dampens enthusiasm for this material.

Dr. Bomford discussed several microbial polysaccharides and compared their activity with that of C. parvum. These materials are less potent activators of macrophages and have considerably less antitumor effect when used intralesionally. Attempts at chemical modification such as oxidation, carboxymethylation, phosphorylation and acylation have not yielded significant increments in therapeutic activity. It seems clear that additional basic research will be required before clinical application beyond that already in progress can be considered.

BCG is of clear therapeutic benefit in patients with only dermal melanoma metastases. Its role in the treatment of other tumors such as ovarian carcinoma, lymphoma, stage 1 non-oat cell carcinoma of the lung and superficial bladder cancer may be validated by trials currently in progress. If a role for BCG in the conventional treatment of cancer can be substantiated, a less toxic substitute would have definite advantages. However, the current limited role of BCG in cancer therapy cannot alone justify an expansion of clinical research with microbial fractions. However, fractionation studies of BCG and other microorganisms show promise of elucidating mechanisms of antitumor action and are deserving of continued support for this reason.

The second day of the workshop was devoted to interferon (IF) inducers. The high cost and scarcity of IF led to a search for IF inducers, a search which has been in progress for more than 10 years. The IF inducers have an additional advantage in that several types of IFs are produced. This mixture of IFs may be more effective than a single type administered exogenously. In addition, the use of IF inducers may achieve higher titers, both systemically and locally at the sites of production, than could be achieved by the administration of exogenous IF. It was soon appreciated that double stranded nucleic acids induced high levels of IF and poly I-poly C was developed and brought to clinical trial. This material not only induced interferon but also enhanced immunity and had a direct antitumor effect. Although toxicity was modest even up to 12 mg/kg/dose, antitumor effects were also modest. This lack of antitumor activity was felt to be due to the short $T_{1/2}$ of poly I-poly C which resulted from a plasma lytic activity. A polycationic shield was built around poly I-poly C to prevent endonucleolytic attack which in turn unzippers the molecule. Thus poly IC LC was developed. Poly IC LC is more stable and retains the ability to induce IF. Unfortunately, it is more toxic than poly I-poly C.

Dr. Arthur Levine at NCI and Dr. Susan Krown at Memorial Hospital have taken this material to clinical

trial. The maximum tolerated single dose (MTD) varies from as little as 1 to as much as 12 mg/M^2. The MTD is related in part to age and other clinical characteristics. However, even in adults with similar clinical profiles the MTD varies widely and is not predictable. Further, there was a wide range of IF produced for any given dose. However, in both studies, doses of 8 mg/M^2 seemed to consistently induce IF at levels that ranged up to 2000 u/ml. Optimal schedule remains to be determined and is complicated by the phenomenon of hyporesponsiveness. This was overcome at least in part in the Memorial Hospital study by progressively escalating dose.

One complete remission in a patient with acute lymphocytic leukemia was noted during the phase 1 trial at NCI. Several phase 2 trials are in progress, each with a different dose and schedule of administration. These seem to have been determined by empiricism enlightened by a prior phase 1 experience and further modified by current experience. One patient with acute myelogenous leukemia sustained a partial remission and one or two patients with multiple myeloma also seem to be responding. This pattern of response is similar to that previously demonstrated for exogenous IF. These responses are not without side effects. Almost all patients become febrile, 75 percent have hematologic toxicity, 50 percent develop nausea and 25 percent become hypotensive.

Attempts to reduce the toxicity of poly I-poly C while maintaining IF inducing properties include enhancing endonuclease degradation by mismatching bases. This procedure did reduce toxicity but a question remains as to whether this readily hydrolyzable material will actually induce IF in man and whether it will show antitumor activity.

Morahan discussed synthetic polyanions including polycarboxylates, polysulfates and polyphosphates. These materials affect a variety of biological functions in addition to their ability to induce interferon. These include antimicrobial and direct antitumor activity, activation of macrophages, effect on NK cells, and adjuvanticity for antibody formation. IF induction by polyanions has been demonstrated in the mouse and man but not in swine, rabbits, rats or guinea pigs. Serum IF concentrations are low reaching only 1-200 u/ml and hyporeactivity occurs. The antitumor and antiviral effects of polyanions do not correlate directly with IF production. For example, the antitumor effect of pyran is only partially abrogated by anti-IF serum.

The third day of the conference was devoted to cancer therapy with synthetic polymers and other synthetic compounds. The session was opened by Dr. Makowka who discussed NED-137, a polymer developed by Monsanto, the structure of which was not revealed. The material has a mean molecular weight of 800 (range 400-1200), is nontoxic and administrable by the oral, intraperitoneal and intravenous routes. The only animal tumor model in which it has been systematically evaluated to date is a transplantable MCA induced bladder cancer in Fisher rats. This is a rapidly growing tumor in that a subcutaneous implant of 0.5 cm diameter reaches several centimeters in size in a few days. If the tumor is not treated, the median survival is two weeks. When animals are treated with a single 30 mg/kg dose of NED-137 median survival was increased to six weeks. The majority of studies were conducted in a model where the tumor is excised on day 7. If no further treatment is administered the tumor recurs locally and lung metastases develop. Untreated, all animals are dead by five weeks. A single treatment on day 0 produces 100 percent survival at 24 weeks. NED-137 is effective over a wide range of doses (0.5-30 mg/kg). Comparative studies were conducted and NED-137 was shown to be superior to a variety of other augmenting agents such as BCG, C. parvum and pyran.

This material is currently under study in other animal tumor models. The effects on the immune system are under investigation but to date have been minimal. There is a 3-5 fold increase in antibody forming cells in the Jerne plaque assay. There is no direct cytotoxic effect on tumor cells.

Falk has used NED-137 clinically at a dose of 30 mg/kg every six weeks orally, intraperitoneally and intravenously in an initial group of 45 patients as part of a phase 1 study. No serious toxicity was noted. Studies with intravenous NED-137 were then expanded to 120 patients with gastrointestinal cancer of all stages. Again little toxicity was noted. Therapeutic benefit was suggested by an attempted comparison of outcome with that of an historical control group. Meaningful conclusions were not possible because of the heterogeniety of the two groups and marked imbalance in important clinical parameters.

In summary, NED-137, MVE2, Bay i 7433 and lipoidal amine have all demonstrated antitumor effect in relevant animal models. The performance of NED-137 in the rapidly growing transplantable rat bladder carcinoma model is impressive. Ease of manufacture of a reproducible product, lack of toxicity in animals and man and ease of administration are all important assets. However, the therapeutic efficacy of this compound requires further assessment in additional, more conventional animal tumor models. The antitumor effects of the lipoidal amine CP46, 665 have been mixed. Lung metastases are reduced in the B16 model but no antitumor effect is demonstrable in the L1210 and P388 systems. Bay i 7433 has demonstrated antitumor effects in a wider variety of animal tumor models when treatment was initiated on days -6 to +2. This suggests a critical dependence on tumor load. Pyran has been most widely tested in animal models. A multitude of biological responses are modified and fractionation has markedly reduced

toxicity. Questions remain regarding the preparedness of Pyran (MVE-2) for clinical development.

The final day of the conference was devoted to miscellaneous substances and began with a discussion of possible immune modulation through regulation of prostaglandin synthesis. Prostaglandins are universal local feedback inhibitors. If the synthesis of prostaglandin is stopped there is an increased response to a variety of normal stimuli. In the early 1970s it was noted that the addition of prostaglandin to certain in vitro assays resulted in depressed T cell proliferation, T cell cytotoxicity, NK activity, ADCC and macrophage function. Prostaglandins are produced by several types of cells, including macrophages and some tumor cells. The addition of prostaglandin synthetase (PS) inhibitors such as intomethacin or aspirin to in vitro immunologic assays produces a mild stimulation of some functions.

Prostaglandin inhibitors can be useful in cancer therapy in four ways:

1) As mild immunostimulants—Indomethacin increases DTH in guinea pigs and patients with combined immunodeficiency disease.

2) As inhibitors of the increased macrophage prostaglandin production induced by some tumors such as murine fibrosarcomas.

3) As inhibitors of prostaglandin production by tumors such as human breast and renal adenocarcinomas—Indomethacin treatment of prostaglandin producing animal tumors results in inhibitions of tumor growth.

4) To inhibit immunomodulator (eg. BCG or C. parvum) induced production of prostaglandin by macrophages—induction of splenic suppressor cells by BCG or C. parvum may be through a prostaglandin mechanism.

Our third and final objective was an assignment of priorities for clinical development. Because of our current inability to quantitatively assess clinical readiness, an assignment of priorities must be largely empirical. Nonetheless, this is an essential step if the Biological Response Modifier Program is to move forward in an orderly fashion.

If a role for microbial agents in the conventional treatment of cancer can be substantiated, a less toxic, consistently uniform, readily quantifiable substitute would offer definite advantages. However, the current limited role of microbial agents cannot alone justify an expansion of clinical research with microbial fractions and preclinical studies to date have not demonstrated a clear therapeutic advantage for fractions over whole organisms. As cited above IF inducers offer several advantages over exogenous IF. The major obstacles to wider clinical application relate to toxicity and the phenomenon of hyporesponsiveness. Additional preclinical research is indicated before expansion of clinical application. The prospect that Type 2 (immune) IF can act synergistically with Type 1 IF in suppressing tumor growth is exciting in view of the encouraging early results with Type 1 IF alone in a variety of human malignancies. At present, the Biological Response Modifiers Program contemplates clinical development of Type 2 IF when adequate supplies of an appropriate material become available. A wide variety of synthetic materials has demonstrated antitumor activity in clinical relevant animal models and/or significant biological response modifying capability.

Pyran (MVE-2) has been most widely tested in animals and for this reason has been empirically selected for clinical development. Aximexone also has been widely tested in animal tumor models and has yielded exciting results in that a clear bell-shaped dose response curve exists and antitumor activity is directly correlated with an increase in cytotoxic "autoreactive" cells.

Board members objected to the $2.75 million in the DCT 1981 budget for development of the BRMP intramural component.

The Board voted to postpone consideration of that segment of the budget until its next meeting after Mihich suggested that was too much money. "If I start a new program I'm lucky to get $1 million," Mihich said. "I would like to suggest that at least $1 million of that go into the grants pocket."

"When we approved the BRMP, we had no details on the intramural component," Board member Sharon Murphy commented.

"I agree with the need for an intramural component," Mihich added, objecting only to its size in the first year.

"Over one fifth of the BRMP budget is going for the intramural portion," Board member Alexander Fefer said. "Neither the Board nor the subcommittee have heard much about it. We need a better feeling of why we need so much, so early."

Robert Oldham, who heads the program, argued that "it is not that much money." The intramural program is developing a facility for clinical testing of biological response modifiers at Frederick Memorial Hospital (Oldham is headquartered at the Frederick Cancer Research Center). "It won't look that excessive when we break it down," with renovation of 22,000 square feet at FCRC, equipping the labs there and developing the 10 bed clinical facility.

Board Chairman Samuel Hellman said, "There is clear sentiment on the Board that we ought to get some presentation on how the $2.75 million will be spent," and postponed further consideration to the next meeting.

CONFEREES AGREE ON SIMPLE EXTENSION OF NCI AUTHORIZATION FOR TWO YEARS

House and Senate conferees on biomedical research authorization bills reached agreement this week on extension of the various authorizations for

two years. The agreement established maximum spending levels for NCI at $1.127 billion for the 1981 fiscal year, including $112 million for cancer control; and $1.232 billion for 1982, including $123 million for control.

The agreement killed the two separate measures approved by each house (the Kennedy and Waxman bills), ending for the next two years in all probability any chance of significant changes in NCI's authorities.

The Senate Health Appropriations Subcommittee has indicated it may turn out a 1981 appropriations bill after all, following speculation after the election that only interim financing through an extension of the continuing resolution now in force would be accomplished before Congress adjourns. The subcommittee is considering adding $20 million to NCI's budget over the $1.001 billion approved by the House.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR DEC., JAN., FUTURE

7th UICC Training Course in Cancer Research—Dec. 1-12, Melbourne

Large Bowel Cancer Review Committee—Dec. 4-5, Prudential Bldg., Houston, open Dec. 4, 7:30—8 p.m.

Metastasis—Pathobiological Aspects with Some Illustrative Clinical Examples—Dec. 4, Roswell Park continuing education in oncology.

2nd Annual Patient Education Seminar—Dec. 6-7, Univ. of California (San Francisco).

Clinical Cancer Program Project Review Committee—Dec. 8-10, NIH Bldg 31 Rm 6, open Dec. 8, 8:30—10 a.m.

President's Cancer Panel—Dec. 9, NIH Bldg 31 Rm 9, 10 a.m., open.

Breast Cancer Task Force—Dec. 9-10, NIH Bldg 1 Wilson Hall, 8:30 a.m. both days, open.

Bladder Cancer Review Committee—Dec. 11-12, Holiday Inn Airport, Arlington, Va., open Dec. 11, 8:30 a.m.—noon.

Cooperative Group Chairmen's Committee—Dec. 16, NIH Bldg 31 Rm 9, 9 a.m., open.

Gynecologic Oncology Group—Jan. 8-10, Miami, semiannual national business meeting.

NAC/NRC Nitrites Committee—Jan. 22, National Academy of Sciences, 2100 C St NW, Washington D.C., 10 a.m.—3 p.m., open. Committee will receive information from individuals and organizations on health risks and benefits of nitrites and on status of research on alternatives.

Current Concepts in Cancer Diagnosis & Management—Jan. 22-24, Century Plaza Hotel, Los Angeles, sponsored by UCLA School of Medicine Surgical Oncology Div. and Jonsson Comprehensive Cancer Center.

UCLA Jonsson Comprehensive Cancer Center Inaugural Scientific Symposium—Jan. 24.

Mechanisms of Metastasis—Jan. 28, Thomas Jefferson Medical College, Philadelphia. Sponsored by the International Cancer Research Data Bank Program and organized by the Cancer Information Dessemination Analysis Center for Virology, Immunology and Biology. Isaiah Fidler, George Poste, Lance Liotta, and Everett Sugarbaker will speak, with Irving Zeidman as moderator. Young scientists, graduate students and postdoctoral fellows are encouraged to present original data at the workshop. Contact CIDAC-VIB, Franklin Research Center, 20th & Race Sts., Philadelphia 19103, phone 215-299-2612.

Div. of Resources, Centers & Community Activities Board of Scientific Counselors—Jan. 29-30, NIH National Library of Medicine, Lister Hill Auditorium, 8:30 a.m. both days, open.

Div. of Cancer Biology & Diagnosis Board of Scientific Counselors—Jan. 29-31, Frederick Cancer Research Center, Bldg 539 First Floor Conference Room, open Jan. 29 and 30, 9 a.m.

Biometry & Epidemiology Contract Review Committee—Jan. 29, NIH Bldg 31 Rm 9, open 8:30—9:30 a.m.

FUTURE MEETINGS

15th Annual Clinical Symposium—Feb. 27-28, St. Jude Children's Research Hospital, Memphis. Open to all physicians who wish to attend, the symposium will present current results in treatment of childhood cancer and leukemia. Emphasis will be given to diagnosis and treatment programs for primary disease as well as to the care of complications. There are no registration fees, but attendance will be limited to approximately 200. Register by writing to Associate Director for Clinical Research, St. Jude Children's Research Hospital, Box 318, Memphis, Tenn. 38101.

Texas Society of Cytology 10th Annual Meeting—March 6-7. Amfac Hotel, Dallas-Fort Worth Regional Airport, cosponsored by Univ. of Texas Health Science Center at Dallas Dept. of Pathology. Lectures, panel discussions and workshops will include cervical intraepithelial neoplasia, lung cancer, benign cervical atypias, diagnostic needle aspirations, variabilities in nongynecologic cytology, and cytological evaluation of malignant lymphoma. Contact Dr. Alice Smith, Dept. of Pathology, UTHSC-Dallas, 5323 Harry Hines Blvd., Dallas 75235, phone 214-688-3345.

19th Annual Conference on Breast Cancer—March 9-13, Hotel Del Coronado, San Diego, sponsored by American College of Radiology, American Cancer Society, College of American Pathologists, Society for the Study of Breast Disease. Contact American College of Radiology, Breast Cancer Conference, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

7th Annual Symposium on Diagnosis & Treatment of Neoplastic Disorders—Medical, Surgical & Radiotherapeutic Aspects—April 2-4, Johns Hopkins Univ. Oncology Center. The course will focus on management of the major types of cancer including lung and colon cancer, malignant melanoma, lymphomas, and gliomas. Seminars will include marrow transplantation, cell kinetics, nutrition, meningeal malignancies, estrogens and cancer, and informed consent. Registration $225. Contact Program Coordinator, Continuing Education, 720 Rutland Ave., Baltimore 21205, phone 301-955-5880.

Oncology Update: 1981—April 25, Century Plaza Hotel, Los Angeles, sponsored by Northridge Hospital Foundation. Discussions on the latest anticancer modalities, current management techniques. Topics will include hyperthermia cancer theory, adjuvant chemotherapy, bone marrow transplantation, Hodgkin's disease—state of the art, and current management of local and disseminated breast cancer. Registration, $125 for physicians, $35 for nurses, $25 students and parapros. Contact Sandra Rozzen, Dept. of Medical Education, Northridge Hospital Foundation, 18300 Roscoe Blvd., Northridge Calif. 91328, phone 213-885-5311.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the Contracting Officer or Contract Specialist named, Research Contracts Branch, National Cancer Institute, Blair Building, 8300 Colesville Rd., Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CM-17402-14

Title: *Manufacture of clinical formulations in soft gelatin capsules*

Deadline: *Approximately Jan. 9*

The Pharmaceutical Resources Branch, Developmental Therapeutics Program, Div. of Cancer Treatment, NCI, is seeking a contractor to develop, manufacture, quality control test, package, label and ship to NCI clinical drug products formulated as liquid-filled soft gelatin capsules.

It is anticipated that the principal (and possible exclusive) product to be manufactured under this contract will be various strengths of delta-9-tetrahydrocannabinol (delta-9-THC) oral capsules. It is expected that 12 formulation projects will be required annually. A formulation project may involve the manufacture of one-half to one million capsules, although greater or lesser amounts may also be required.

All work performed under this contract must be in accordance with Food & Drug Administration promulgated Current Good Manufacturing Practices and all pertinent Drug Enforcement Administration rules and regulations for Schedule I substances.

The contractor selected must meet at least the following minimum requirements:

1. Must be currently engaged in soft gelatin capsule manufacturing and will be required to have operational equipment and capabilities at the time of contract award.

2. Must possess a DEA Schedule I manufacturing license or provide documentation that such license can be readily obtained.

3. Must have inhouse capability to perform the following: gas liquid chromatography, high pressure liquid chromatography, ultraviolet and infrared spectroscopy, melting point, moisture and pit determinations, titrimetric analysis, paper and thin layer chromatography, dissolution and disintegration determinations.

4. The facility must be located within the 48 contiguous states of the United States.

Contract Specialist: Susan Hoffman
Cancer Treatment
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RFP N01-CP-05714-58

Title: *Resource for transplacental carcinogenesis studies in primates*

Deadline: *Jan. 2*

The Laboratory of Experimental Pathology, NCI, requires the services of a private laboratory to continue a collaborative research program now in progress on perinatal carcinogenesis in nonhuman primates. The facility will be used for maintenance, breeding (including timed mating), carcinogen treatment, and necropsy of animals comprising a colony of approximately 200 juvenile and adult erythrocebus patas monkeys, together with smaller numbers of infants, and must be physically separate from all other species which may be housed in the same building.

A common cage washing area is acceptable if clean equipment does not traverse areas inhabited by other species. In this facility, animals must be housed in multiple closed rooms with independent air handling configurations that meet specifications of the NIH standards applicable to primates. One room must have capacity to operate 12 isolation chamber units at 15 air changes/hr. The facility must have AALAC accreditation.

In support of the primate holding function of this facility, there should be a general biochemical laboratory room and surgical/necropsy facility immediately adjacent to the holding area. The government will provide caging and surgical suite furnishings.

A veterinarian board-certified or board eligible in laboratory animal medicine and a principal investigator (these may be the same individual) will be required, parttime, to supervise the technical and animal care staff, diagnose and treat any medical problems in the animals, and participate actively in the research projects performed at the facility in accordance with protocols provided by the project officer. The principal investigator will supervise or perform administration of chemical carcinogens and other substances; removal of tissue samples; and surgical operations, including cesarean sections, laparatomies, and procedures for removal of induced tumors from sites other than intracranial or intrathoracic.

Protocols will be phased in so as to maintain the colony size at a maximum of 200 adult and weaned juvenile animals.

The contractor's personnel must be available to NIH staff on a 24 hour basis and the facility should be accessible to NIH staff several days a week. This requirement addresses the labile nature of chemicals to be used and the need for rapid transport of fresh, viable tissue for cell culture studies at NIH. These requirements define the contract specifically as a resource supporting the Carcinogenesis Intramural Research Program of NCI. Therefore, potential offerors must be located within 35 miles of the NIH reservation in Bethesda, Md.

Contract Specialist: Mary Armstead
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The Cancer Letter _Editor Jerry D. Boyd

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