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

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NEW NCI GRANT PROGRAM WILL SUPPORT YOUNG SCIENTISTS IN INNOVATIVE, "RISKY" RESEARCH

NCI will start a new grant program to support early stages of cancer-relevant research by young investigators in the 1978 fiscal year, with from $500,000 to $1 million to be made available to fund from 25 to 50 individual awards.

The program, called New Initiative Awards, will provide support for up to three years, not to exceed $25,000 a year in direct costs. No more than $15,000 a year may be paid to the principal investigator for salary.

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In Brief

GSA SITTING ON BREAST CANCER TAPES; CREECH, OWENS NAMED PRESIDENTS-ELECT OF AACR, ASCO

BUREAUCRATIC NONSENSE by the General Services Administration is holding up distribution of the videotape NCI made of the "Report to the Profession" breast cancer conference held last November. NCI intends to make the 6-hour tape available to professional groups, schools, hospitals, etc. for continuing education classes. David Prowitt of Medical Science Programs Inc. had the master tape ready to go on schedule three weeks after the conference. GSA then got in on the act, in handling the contract to make duplicate tapes. Six months later, the contract still has not been awarded. . . . **HUGH CREECH**, who is retiring after 25 years as secretary-treasurer of American Assn. for Cancer Research, was elected vice president and president-elect at the Denver meeting. AACR added 225 new active members this year: total membership now is 2,701. **GORDON ZUBROD**, director of the Florida Comprehensive Cancer Center and former director of NCI's Div. of Cancer Treatment, is the current AACR president. . . . **AL OWENS**, director of the Johns Hopkins Comprehensive Cancer Center, is president-elect of the American Society of Clinical Oncology. Vincent DeVita, present director of the Div. of Cancer Treatment, is this year's president. ASCO membership has grown 25% in the past year, now stands at 1,500. More than 2,000 registered for the annual meeting. . . . **HOUSE HEW** Appropriations Subcommittee gave NCI $831.9 million in the markup of its money bill, an increase of only $16 million over the current year's budget. The subcommittee earmarked $11 million for traditional grants, $2 million for training. Rep. David Obey also wrote in another 22 positions for environmental epidemiology and environmental pathology. . . . **UNIV. OF ALABAMA'S** problem in getting its staff to work with community physicians in a pediatric cancer program (***The Cancer Letter***, May 20) apparently has been solved. John Durant, director of the Comprehensive Cancer Center, said a new chief of the pediatric program who will work with community doctors is being recruited.

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NEW GRANT PROGRAM LIMITED TO YOUNG SCIENTISTS WITH NO PRIOR NIH AWARDS

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New Initiative Awards will be available only to investigators who have received a doctoral degree within a four year period prior to submitting an application or have completed a clinical residency program within two years prior to submitting an application. No one who has received an NIH Research Career Development Award or who has been the PI on any NIH grant or contract will be eligible.

Harold Amos, member of the National Cancer Advisory Board, presented the new program to the Board for its concurrence Monday. The program outline was drafted by Barbara Sanford, chief of the Cancer Biology Branch in the Div. of Research Resources & Centers.

Amos said the program "has certain elements of risk" but felt it should be given a try.

Sanford pointed out that "even though overall statistics show investigators under 35 faring well in competition for RO1 traditional research grants, program directors attending study sections as well as members of the outside community have become increasingly concerned about apparent reluctance of study sections to assign high priority to relatively untried young investigators with interesting new ideas, or in fact to established investigators seeking to veer off into approaches outside their recognized areas of experience. In times when grant funds are limited, there seems to be a tendency for study sections to favor what is sometimes called 'establishment science' over more risky new approaches."

Sanford's proposal would have made the awards available, in addition to young, new investigators, to "established investigators embarking on new research ventures outside their established areas of experience."

But Benno Schmidt, chairman of the President's Cancer Panel, objected to "encouraging people to leave the fields they are in to come into a field where we are funding only 30% of approved grants." Schmidt also cited the fact that investigators under age 35 were doing all right in competing for traditional grants.

Amos said that in reviewing study section actions, he has seen where "time after time interesting new ideas were presented, but with certain amount of risk. They get priority ratings of 300 because it is a risk," and thus are seldom funded.

"Because money is tight is precisely why this program is being considered," Sanford said. "A study section will say, 'Okay, this is an exciting proposal, but this investigator doesn't have a track record,' and since money is tight, the investigators with established records get funded."

When Schmidt insisted that the program should not be used to encourage established investigators in other fields to switch to cancer, Sanford agreed to drop that part of the proposal.

Board member Denman Hammond suggested that the program might be tailored to reach even younger scientists, before they are 30 "when they make the critical career decisions" on their career goals. NIH training grants helped serve that function before they were phased out, Hammond said.

Board Chairman Jonathan Rhoads compared the New Initiative Awards to professional football's draft of new players.

"I've never been in favor of a draft of people over age 40 who have never played football," Schmidt responded.

The Board did not take a vote on the plan, but DCRRC Director Thomas King said after the meeting, "I didn't hear anyone say we couldn't do it." King said he hoped the program could be implemented for funding in FY 1978, which starts next Oct. 1.

Sanford noted that other NIH institutes have been using similar programs "which have been very successful." She also referred to the American Cancer Society's new small grants program to provide rapid funding for critical, urgent needs (***The Cancer Letter***, April 15). "This is a different type of problem than that which would be addressed by the proposed New Initiatives Awards, and the two programs should complement each other," she said.

If NCI moves quickly enough, the first deadline for applications will be Nov. 1. The first awards would then be made by May, 1978.

To be eligible, projects must be relevant to the cause, prevention, diagnosis, treatment or biology of cancer; must involve exploratory research with analysis of associated findings; must be designed so that preliminary studies can be completed in three years or less; and must be acceptable in accordance with recognized criteria for scientific merit.

Both basic and clinical research projects are encouraged, providing that they have clear relevance to carcinogenesis, clinical oncology, detection and diagnosis, drug development, epidemiology, immunology, radiation therapy, radiation biology and physics, tumor biology, or viral oncology.

OAT CELL CARCINOMA, HEAD AND NECK CANCER TREATMENT ADVANCES REPORTED

Major advances in treatment of oat cell carcinoma of the lung and head and neck cancer were reported at the scientific sessions of the American Society of Clinical Oncology annual meeting.

"There is no question that a cure is now available for this previously incurable disease," said ASCO's new president, Vincent DeVita, referring to papers on oat cell carcinoma presented by members of his staff and NCI's Div. of Cancer Treatment and other investigators.

Harmar Brereton, C. Harry Kent and Ralph Johnson of NCI reported more than a year ago the results they were achieving with intensive combined chemotherapy and radiotherapy of small cell lung cancer. Their ASCO paper updated those results in which 33 of 50 patients entered in the study achieved complete remission and 36% have had disease free survival exceeding 27 months.

The treatment regimen is extremely toxic, and Johnson was considerably distressed last year when he was besieged with requests from physicians, patients and their families for details after his early results received widespread publicity.

"There is no doubt that the toxicity of these regimens is formidable," the scientists said in their ASCO presentation, "but we feel that substantial gains in the treatment of small cell lung cancer cannot be made without this type of approach. Certainly as we have gained experience with concurrent therapy the incidence of fatal treatment-related complications has diminished, and refinement of these treatment techniques will further diminish these complications."

Fifty previously untreated patients with biopsy proven small cell lung cancer were admitted to the study between November 1974 and November 1976. At the completion of staging, 29 patients were classified as having clinically detectable disease confined to the chest–termed "intrathoracic disease." The remaining 21 were classified as having disease metastatic outside of the chest–"extrathoracic disease."

Chemotherapy consisted of cyclophosphamide 1500 mg/M^2, adriamycin 40 mg/M^2 and vincristine 2 mg all given intravenously on the same day and repeated as soon as the white blood count had recovered to 3500/mm^3. The mean interval between chemotherapy treatments was 21 days. Patients with extrathoracic disease received a mean of 4.3 cycles, and patients with intrathoracic disease received a mean of 4.0 cycles.

Chemotherapy was given concurrently with the chest irradiation in the first four groups and prior to chest irradiation in the last group. Two thousand to 3,000 rads of whole brain prophylactic irradiation was given concurrently with chemotherapy in all patients.

Between nine and 11 patients were admitted to each radiation therapy regimen consisting of first, 200 rad fractions daily, five days a week to 3,000 rads; second, 200 rad fractions three times daily for five consecutive days to 3,000 rads; third, 100 rad fractions daily for five days a week to a total dose of 3,000 rads; fourth, 200 rad fractions three times daily for one day two weeks after receiving chemotherapy to a total dose of 3,000 rads; and fifth, 150 rad fractions daily five days a week, split course to a total dose of 4,500 rads.

With completion of therapy, response was evaluated and patients achieving a complete response were followed without further treatment. Complete remission was defined as a normalization of all initially abnormal parameters of the disease, partial remission as a greater than 50% reduction of all measurable tumor, and no response as anything less than a 50% reduction.

Twenty-three of 29 patients with intrathoracic disease and 20 of 21 with extrathoracic disease had complete remissions. Partial remissions were noted in four patients, and three did not respond.

Five patients with intrathoracic disease and five with extrathoracic disease died during the induction phase from treatment-related complications. Five of the 10 had no tumor at autopsy.

The median survival of patients with extrathoracic disease was only 10.5 months and by 18 months none of those patients was disease free.

None of the 33 patients who achieved complete remission relapsed primarily in the brain. "This appears in distinct contrast to the experience of most investigators who find upward of 20% of initial relapses in the brain," the scientists reported.

Hematologic toxicity from concurrent chemo/radiotherapy was contrasted with toxicity noted from sequential chemo/radiotherapy. The white blood cell nadirs were 600/mm^3 in the former group and 900/mm^3 in the latter group. The median polymorphonuclear leukocyte nadirs were 150/mm^3 and 500/mm^3 respectively. The median platelet nadir of 69,000 with concurrent therapy was substantially lower than the median nadir of 173,000/mm^3 for patients with sequential therapy.

Infectious complications included one patient with bacterial sepsis, eight with perirectal infections (two with sepsis), seven with pneumonia (one with sepsis) and one with an infection at the site of a central venous catheter. Seventeen of the 50 had at least one serious bacterial infection.

Drug enhanced radiation reactions included treatment-related dermatitis, with 72% of the patients having some degree of skin desquamation; 70% had moderate or severe esophagitis and three developed esophageal strictures; 20% had treatment related pneumonia which was fatal in three cases.

"The radiation therapy schedules which proved most toxic when combined with chemotherapy have been those utilizing 200 rad fractions, and particularly those in which patients were treated more than once a day," the report said.

Central nervous system toxicity occurred within three months of starting brain radiation therapy and resolved within six months. It has occurred in 42% of the patients; symptoms include memory loss, somnolence, tremor, slurred speech and myoclonus. "The syndrome produces only mild disability usually and remits completely," the report said.

There were no cardiac or spinal cord toxicity from the treatments.

Lawrence Einhorn, Ned Hornback and William Bond of Indiana Univ. Medical Center reported on

their study using combination chemotherapy, radiotherapy and immunotherapy in small cell undifferentiated lung cancer.

Fifty eight patients treated from September 1974 to March 1976 were treated with adriamycin 50 mg/M^2, cytoxan 750 mg/M^2 and vincristine 1.5 mg. was given on day one and continued every three weeks, but with a 20% reduction of subsequent ADR and CTX dosages. At the completion of 450 mg/M^2 of ADR, chemotherapy then consisted of CCNU 50 mg/M^2 orally every six weeks, CTX 500 mg/M^2 orally every three weeks, and methotrexate 20 mg/M^2 orally weekly. Split courses of XRT were given to the lung primary and prophylactic whole brain (300 rads for six days) starting on days 22 and 50. BCG was given one and two weeks after each chemotherapy course.

Toxicity consisted primarily of nausea, vomiting, alopecia, and mylosuppression. The median lowest granulocyte count was 1100, but only five patients developed granulocytopenic infections. There were 26 partial and 23 complete remissions. The median duration of partial remissions was 26 weeks and complete remissions 54 weeks with 11 patients remaining in complete remission. There was only one CNS relapse. The median survival was 51 weeks with 19 patients remaining alive from 39 plus to 113 plus weeks.

Intensive preoperative chemotherapy for head and neck cancer has been developed in a number of studies to shrink tumors and permit less disfiguring surgery. An NCI team has used extremely high doses of methotrexate followed by leucovorin rescue in a study of 10 elderly patients, achieving 50% reduction of tumor mass in four of five previously untreated patients (this study was reported to the Div. of Cancer Treatment Board of Scientific Counselors, (***The Cancer Letter,*** March 25). The scientists—N.H. Goldberg, Paul Chretien, E.G. Elias, K.R. Hande, Bruce Chabner and C.E. Myers—presented their findings at the ASCO meeting.

Patients received two weekly courses of MTX as an initial IV bolus followed by a 36 hour infusion of 1500 mg/M^2. MTX plasma levels were closely monitored. Leucovorin was given as a 25 mg/M^2 IV push followed by a constant infusion of 200 mg/M^2 IV for 12 hours and then 25 mg/M^2 IM every six hours for six doses. No patient developed renal toxicity, two of 20 infusions were associated with transient leukopenia without significant infection. Thrombocytopenia without bleeding occurred after one infusion. Transient rises in hepatic transaminases were seen in six of 17 monitored infusions.

All patients underwent surgical resection of remaining tumor within one to three weeks following the second MTX infusion.

"This high dose regimen appears well tolerated in this elderly patient group and is being used in further trials of intensive preoperative therapy," the NCI scientists reported.

A team at Northwestern Univ. reported on methotrexate with leucovorin as an adjuvant to surgery and radiotherapy in locally advanced squamous carcinoma of the head and neck.

The team—S.G. Taylor, IV; D.E. Bytell and G.A. Sisson—reported that a two week course of MTX and leucovorin was given to 17 stage III and IV patients prior to surgery and/or radiotherapy. Dosage of MTX was 60 mg/M^2 i.m. q6hx4 followed in 6h by L 40 mg p.o. q6hx2 then 10 mg q6hx6 with treatments repeated on days 5 and 9. The dosage of MTX was escalated 50% each treatment if no mucosis existed and WBC was greater than 4000/mm^3 and platelets greater than 125,000/mm^3. Mucositis was the usual dose limiting toxicity with 10P (59%) having oral ulcerations during ML. Lowest WBC was 2500/mm^3 and lowest platelets 51,000/mm^3. Radiotherapy immediately after chemotherapy in four patients produced earlier mucositis with all patients receiving approximately 7,000 rads to tumor over 59 to 73 days.

No surgery related toxicity from the drugs was noted but one patient died on day 11 from pulmonary embolism. Three of six stage III patients remain with no evident disease at 21, 22 and 38 months. One patient recurred at 12 months and two developed second primaries at 12 and 27 months. Seven of 11 stage IV patients remain with no evident disease with one post-op death, one recurrence at nine months and one with a second primary.

Of the total patients, two of 12 have died and two are living with tumor. Thirteen are free of disease.

"These results are superior to other methotrexate adjuvant programs despite very advanced disease and suggest that MTX dose escalation to toxicity may be important for maximal adjuvant effect," the scientists reported.

In the NCI study, five patients had been previously treated with radiation. None of them had the 50% tumor size reduction noted in four of the five previously untreated patients. A team at Memorial Sloan-Kettering, using a combination of drugs followed by radiation therapy, offered an explanation:

"In the past, only 20 to 30% of patients with advanced head and neck cancers responded to therapy," commented Victor Randolph, one of the Memorial Sloan-Kettering team. "Generally these drugs were given following radiation failure in patients in whom the cancer was too advanced for surgery. It may be that drugs were ineffective in the past partly because radiation damages tumor circulation and hence the flow of drugs to the cancer. In fact, the same combination of drugs was less effective with patients who had been previously irradiated."

Other members of the team are Alvaro Vallejo, Elliot Strong and Robert Wittes. Their study involved 21 patients with various head and neck cancers that were too advanced for surgery and had

not been treated before. They were given high doses of cis-platinum, and standard amounts of bleomycin, followed by radiotherapy. The platinum was administered IV, followed two days later by seven days of bleomycin, another platinum injection and radiation. Because cis-platinum in large doses is highly toxic to the kidneys, mannitol, a diuretic, was given to flush the drug from the system before serious damage to normal tissue could occur.

Twenty patients had shown some response to therapy by the end of the drug phase and before radiation began. Of the 16 patients who have now completed both phases of the treatment, 12 were still responding at the end of therapy, and six were entirely free of clinically detectable cancer. Four patients are still in remission.

HOPKINS INVESTIGATOR DIES IN FALL FROM HOTEL WINDOW AT ASCO MEETING

For Geraldine Konior Yarbro, her professional and private life had been on the upswing. Last January, she became the wife of John Yarbro, director of the Missouri Cancer Program and former director of NCI's Cancer Centers Program. And on May 17, she had presented a highly-praised paper at the annual meeting of the American Society of Clinical Oncology which grew out of her work with Brigid Leventhal at Johns Hopkins Oncology Center.

A few hours after accepting congratulations for the paper, Geraldine Yarbro was killed in a fall from the window of the 15th-floor hotel room in Denver she was sharing with her husband. Yarbro was scheduled to present his own paper the next day at the meeting of the American Assn. for Cancer Research.

Yarbro told police his wife had stumbled and fell against the floor to ceiling window. The window broke and she fell through, he said. She was clad in the black evening gown she had worn to a reception for ASCO members and guests.

Mrs. Yarbro was an MD in pediatric oncology at Hopkins. She had planned to join her husband in Missouri upon completion of the fellowship.

The paper Mrs. Yarbro presented was titled, "Correlation of Glucocorticoid Receptor Levels and Complete Remission Duration in Poor Prognosis Acute Lymphatic Leukemia." Coauthors in addition to Leventhal were M.E. Lippman and G.E. Johnson. The abstract of the paper follows:

Viable lymphoblasts from 45 children with ALL were quantitatively assayed for GR using a competitive receptor binding assay. Surface marker studies were also done. We have previously reported that T blasts have significantly lower levels of GR than null blasts. Analysis of CRD suggests that the level of GR can serve to further subcategorize these groups of pts. GR levels correlated with cell type and initial CRD, as shown below.

Marker	GR sites/cell	Med. CRD (mo)	In Cr
T	<2500	7.6	0/11
T	2501-<6,000	18.5	3/7
Null	2501-<6,000	22.7	2/11
Null	>6,000	N.R.>26.0	10/16

Pts with T cell ALL and low GR levels had a short CRD. Pts with T and Null ALL and intermediate GR levels had an intermediate and identical CRD. The best CRD was in null ALL with high GR levels. 21 of these pts with initial WBC >20,000 are shown below with median age, white count and CRD.

Marker	GR sites/cell	Age	WBC	CRD(mo)	In Cr
T	<6,000	13.8	80.	8.0	0/9
Null	<6,000	5.0	84.	8.0	0/5
Null	>6,000	4.5	67.	25.0	3/7

Although both null groups were equivalent in age and WBC, those with <6,000 GR did as poorly as those with T cell ALL. These studies indicate that GR levels have clinical significance independent of age, WBC and cell type and are a useful additional prognostic indicator in ALL.

ABSTRACTS OF 'MOST NEWSWORTHY' PAPERS PRESENTED AT AACR MEETING

The various subcommittees of the Program Committee for the 68th annual meeting of the American Assn. for Cancer Research selected 17 papers they considered to be "newsworthy." Papers chosen included reports on research in virology, experimental chemistry, clinical investigation and clinical chemistry, and carcinogenesis. None were selected for biology, immunology or biochemistry. Abstracts of the papers selected follow here and in subsequent issues of *The Cancer Letter.*

VIROLOGY

SITES OF INTEGRATION OF HERPES SIMPLEX VIRUS (HSV) THYMIDINE KINASE (TK) GENE IN TRANSFORMED HUMAN CELLS – Ludvik Donner, Saul Kit, Baylor College of Medicine

The purpose of this study was to determine the chormosomal site(s) of integration of the HSV TK gene in TK^- human HeLa (BU25) cells that had been biochemically transformed by UV- inactivated HSV type 2. Human-mouse (HL) somatic cell hybrids were isolated by fusion of ouabain-sensitive, TK^+ HSV-2 transformed human [HeLa(BU25)/HSV-2 Clone 4] cells with ouabain-resistant, TK^- LM(TK^-) mouse fibroblasts in selective HAT-ouabain medium. It was shown that the HL lines expressed HSV-2 TK by 3 methods: (i) disc PAGE analyses; (ii) enhancement of the resident TK activity by superinfection with TK^- HSV mutants; and (iii) neutralization with anti-HSV-2 TK-specific antisera. Karyological analyses by the G-banding technique revealed that all the hybrid HL lines and subclones tested contained a complement of mouse LM(TK^-) chromosomes and a few human chromosomes. Twelve of 12 HL-1 mitoses contained human chromosome 17 and one contained a HeLa marker chromosome. However, 17 of 19 HL-2 mitoses contained human chromosome 12, and 1-7 additional human chromosomes, but not chromosome 17. Thirteen of 19 HL-2 mitoses contained human chromosome 7. Karyological analyses of subclones and counterselected clonal lines are in progress. The results suggest that the HSV-2 TK gene is integrated at different chromosomal sites in HeLa(Bu25)/HSV-2 Clone 4 cells.

INFECTIOUS HUMAN AND NON-HUMAN PRIMATE RNA TUMOR VIRUS PROVIRAL DNA IN PRODUCTIVELY INFECTED CELLS – Phillip Markham, Robert Gallo and Prem Sarin, Litton Bionetics and NCI.

Applying conventional transfection methods, we are able to routinely infect competent target cells using DNA purified from human and non-human primate RNA tumor virus producing cells. These include cells producing simian sarcoma virus (SSV), and the two components of a virus (HL23V) isolated from huma leukemia cells, HL23V (SSV-related), HL23V baboon endogenous virus-related, or cells producing both components.

Using cells preselected for ability to support growth of either SSV, BaEV, or HL23V as recipients, we tested standard stocks of DNA for

ability to transfect their respective viral information. We find notable differences in the relative sensitivity of the various recipient cells to transfection by a given source of DNA. Based on these studies, it is apparent that one cannot always predict the most sensitive target cell to use in transfection studies based solely on its support of virus growth. This becomes particularly important when proviruses of uncharacterized viruses are being sought, e.g., those reported in human tissues.

The application of the primate virus transfection technology to detection or isolation of viruses in human materials and its use in monitoring enrichment of provirus by various biochemical procedures and effect of restriction endonucleases on the activity of specific proviruses will be discussed.

IN VITRO CYTOTOXICITY OF CYTOSINE ARABINOSIDE ENTRAPPED IN PHOSPHOLIPID VESICLES – Eric Mayhew and Demetrios Papahadjopoulos, Roswell Park Memorial Institute.

The anti-leukemic drug cytosine arabinoside (ARA-C) and some phosphorylated derivatives were entrapped in a series of different types of phospholipid vesicles. Comparisons were made between the effectiveness of the drug entrapped in these vesicles against L1210, ELD ascites, 3T3 SV40 transformed cells in vitro, compared to the "free" drug and to the "free" drug used in combination with non-drug containing vesicles. The different vesicles used were positively or negatively charged, fluid or solid, multilamellar or small (<1000 Å diameter) and large unilamellar (>1000 Å). Different vesicle drug combinations gave a ID_{50} somewhat different from the value for the free drug. ARA-C entrapped in positively charged fluid small and unilamellar vesicles was 2-3 times more effective than the free drug. ARA-CTP, presumably the biologically active moiety of ARA-C, when entrapped, particularly in positively charged vesicles was effective at concentrations considerably less than that required for the free ARA-CTP indicating that the highly charged molecule when entrapped, indeed got transported across the membrane barrier, without degradation.

ALTERATIONS IN FUCOSE METABOLISM OF SARCOMA 180 CELLS BY 6-thioguanine (6TG) – John Lazo and Alan Sartorelli, Yale Univ. School of Medicine

Previous studies from our laboratory have shown that exposure of Sarcoma 180 cells to 6TG in vitro results in surface alterations detected by Concanavalin A (Con A) agglutination. A significant decrease in ^{3}H-fucose incorporation into acid-precipitable material from Sarcoma 180 was observed 1-6 hr after treatment of tumor-bearing mice with 20 mg 6TG/kg; maximum reduction of 70% occurred at 2 hr. Under identical conditions, no decrease in ^{14}C-glocosamine incorporation was produced by 6TG. Inhibition of ^{3}H-fucose incorporation was dose-dependent and reached a plateau at 10 mg 6TG/kg. In 6TG-resistant cells (Sarcoma 180/TG), ^{3}H-fucose incorporation into acid-insoluble material 2 hr after 10 mg 6TG/kg was reduced only 30%. Radioactivity from fucose in acid-soluble extracts was significantly decreased in Sarcoma 180, but not in Sarcoma 180/TG 2 hr after 10 mg 6TG/kg. Hot ethanol extracts of Sarcoma 180 cells treated with 20 mg 6TG/kg contained less GDP-fucose/cell than untreated cells. Although no reduction in Con A binding occurred at 2 hr after 6TG, we observed decreased ^{3}H-Con A binding to Sarcoma 180 cells 12 hr after 20 mg/kg of 6TG.

Results indicate 6TG inhibits addition of exogenous fucose to macromolecules and reduces lectin binding. These actions may be associated with 6TG cytotoxicity to neoplastic cells.

EFFECTS OF TOCOPHEROL ON ADRIAMYCIN-INDUCED CARDIOMYOPATHY AND TUMOR RESPONSE – W. McGuire, R.C. Young, K. Grotzinger and C.E. Myers, NCI

Production of free radicals (FR) occurs in vitro when Adriamycin (ADR) is incubated with heart mitochondria and FR-induced damage to cardiac lipids occurs in mouse and rabbit hearts exposed to ADR in vivo. Several FR scavenging agents were used to attempt to block both acute and chronic ADR-induced cardiac toxicity in CDF_1 mice. Of several agents, only α-Tocopherol (α-T) was effective in decreasing toxicity. α-T was used in several schedules and found most protective as a single I.P. dose of 85 I.U. per mouse 24 hours prior to ADR. Partial protection was shown with single doses of 7.5 mg/kg to 15 mg/kg ADR in the acute model. The chronic model used 5 mg/kg ADR weekly and protection was also seen (ADR alone = LD_{85}; ADR and α-T = LD_{10}). Response of P388 ascites tumor to ADR was not changed by α-T and even allowed for administration of curative doses of ADR not normally tolerated due to toxicity. Pathologic parameters of cardiac damage were less frequent or severe after α-T treatment. Biochemical determinants of FR production (malondrialdehyde, etc.) were significantly ($p=0.01$) less in animals treated with α-T.

α-T is capable of ameliorating both the acute and chronic ADR-induced cardiomyopathy of mice without impairing antitumor activity.

CARCINOGENESIS

VITAMIN A ACID (RETINOIC ACID), A POTENT INHIBITOR OF 12-0-TETRADECANOYL-PHORBOL-13-ACETATE (TPA)-INDUCED ORNITHINE DECARBOXYLASE (ODC) ACTIVITY IN MOUSE EPIDERMIS – A.K. Verma, J.W. Holder, and R.K. Boutwell, McArdle Laboratory, Univ. of Wisconsin

As part of the studies of factors modifying skin tumor promotion by TPA, we found that the topical application of an antitumorigenic agent, retinoic acid, inhibits TPA--induced soluble mouse epidermal ODC activity, an event proposed to be essential for tumor promotion.

The degree of inhibition was dose and time dependent: 3.4 and 0.17 nmoles applied 1 hr before TPA (17 nmoles) treatment inhibited 100 and 57% respectively; 1.7 nmoles of retinoic acid applied either 2 hr before or 2 hr after TPA treatment inhibited more than 70%, while treatment 18 hr before or 3 hr after was almost ineffective. Retinoic acid treatment did not depress S-adenosylmethionine decarboxylase induction. Furthermore, retinoic acid did not alter TPA-induced epidermal ODC activity when added to the assay mixture. A number of natural and synthetic retinoids were evaluated for their ability to inhibit TPA-induced mouse epidermal ODC activity; retinoic acid and its cyclopentenyl analogs were the most potent inhibitors, whereas a furyl analog of retinoic acid was almost devoid of activity.

These results suggest that retinoids can be used as a tool for the study of the role of polyamine biosynthetic enzymes in skin tumor promotion, and inhibition of TPA-induced epidermal ODC activity may be a specific and rapid test for antitumorigenic properties of retinoids.

ADVISORY GROUP, OTHER CANCER MEETINGS FOR JUNE, JULY

Combined Modality Committee—Scheduled for May 31-June 1, canceled.

Symposium on Etiology, Diagnosis & Treatment of Non-Hodgkin's Lymphomas—June 1, Yale Univ., contact Alan Lebowitz or Marion Morra.

National Prostatic Cancer Project Working Cadre—June 1, Roswell Park, open 8:30–9 a.m.

Clinical Cancer Education Committee—June 1-2, Linden Hill Hotel, Bethesda, open June 1, 8:30–9:30 a.m.

Second International Symposium on Cancer Therapy by Hyperthermia & Radiation—June 2-4, Essen, Germany.

Cancer Control Intervention Programs Review Committee A—June 2-3, Blair Bldg. Room 110, open 8:30–9 a.m. both days.

Management of All Stages of Colorectal Carcinoma—June 4, Roswell Park continuing education in oncology, contact Claudia Lee.

President's Cancer Panel—June 7, NIH Bldg 31 Room 7, 9:30 a.m., open.

Present Status of Management of Prostate and Bladder Cancer—June 9, Roswell Park continuing education in oncology.

Workshop on Graduate Education in Oral Oncology—June 13-14, Bethesda Holiday Inn, 8:30 a.m., open (co-sponsored by NCI's Div. of Cancer Research Resources & Centers and the National Institute of Dental Research).

Cancer Control Grant Review Committee—June 13-14, NIH Bldg 31 Room 7, open June 13, 8:30–9 a.m.

Clinical Cooperative Group Chairmen—June 14, NIH Bldg 31, Room 8, 9 a.m., open.

National Bladder Cancer Project Working Cadre—June 14, Logan Airport Hilton, Boston, open 8:30–11 a.m.

Cancer Control Community Activities Review Committee and Grant Review Committee, Joint Meeting—June 15, Blair Bldg Room 110, open 8:30–9 a.m.

Committee on Cancer Immunotherapy—June 15-17, Landow Bldg Room C418, open June 15 7:30–8 p.m.

Virus Cancer Program Advisory Committee—June 16-17, NIH Bldg 37, Room 1B04, 9:30 a.m. both days, open.

Cancer Control Community Activities Review Committee—June 16, Blair Bldg Room 110, open 8:30–9 a.m.

National Large Bowel Cancer Project Working Cadre—June 16-17, Houston Anderson Mayfair, open June 16, 7:30–8:30 p.m.

Fourth Annual National Cancer Communications Conference—June 20-21, Chicago Pick Congress Hotel.

Cancer Special Program Advisory Committee—June 20-21, NIH Bldg 31 Room 8, open June 20, 9–10 a.m.

Committee on Cancer Immunobiology—June 21, NIH Bldg 10 Room 4B14, open 2–2:30 p.m.

National Clearinghouse on Environmental Carcinogens, Subgroup on Chemical Selection—June 22, NIH Bldg 31 Room 10, 8:30 a.m., open.

Clearinghouse Experimental Design Subgroup—June 23, NIH Bldg 31 Room 7, 8:30 a.m., open.

Developmental Therapeutics Committee—June 23-24, Blair Bldg, open June 23, 9–10 a.m.

Carcinogenesis Program Scientific Review Committee A—June 23-24, Twin Bridges Marriott Hotel, Arlington, Va., open June 23, 9–9:30 a.m.

Clinical Cancer Investigation Review Committee—June 27-29, NIH Bldg 31 Room 6, open June 27, 9–10 a.m., June 28, 8:30 a.m.—noon for minisymposium on toxicity of combined modality treatment.

Committee on Cancer Immunodiagnosis—June 28, NIH Bldg 10, Room 4B14, open 1–1:30 p.m.

President's Cancer Panel—July 12, NIH Bldg 31 Room 7, 9:30 a.m., open.

General Oncology & Hematology—July 18, Roswell Park continuing education in oncology.

(Additional listings for July will appear in ***The Cancer Letter*** *June 24.)*

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. Their addresses, all followed by NIH, Bethesda, Md. 20014, are:
Biology & Diagnosis Section — Landow Building
Viral Oncology & Field Studies Section — Landow Building
Control & Rehabilitation Section — Blair Building
Carcinogenesis Section — Blair Building
Treatment Section — Blair Building
Office of the Director Section — Blair Building
Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CB-74172-39

Title: *Administrative support services for the Div. of Cancer Biology and Diagnosis of NCI*
Deadline: *July 7*

NCI is interested in awarding a contract to provide adminstrative support services in the conduct of scientific conferences, meetings, and workshops on cancer research and related activities. The contractor shall furnish all necessary personnel, labor, facilities and equipment, materials and supplies except as may otherwise be provided by the government.

Offeror must have working experience in the specific type of services involved. Offeror must also be capable of "quick-reaction" response to the tasks designated and conferences scheduled, and must have qualified personnel to perform such tasks.

Contracting Officer: Harold Simpson
Biology & Diagnosis
301-496-5565

RFP DU-77-B169

Title: *Mutagenicity studies of environmental chemicals using in vitro and in vivo bioassays*
Deadline: *To be determined*

The contractor shall provide the capability for testing chemicals for mutagenic potential. Chemicals shall be screened in a variety of test systems, including bacteria, yeast, mammalian cells in culture, Drosophila and additional suggested in vivo tests using Tradescantia and mice.

Environmental Protection Agency
Contracts Management Div.
(MD-33) Office of Admin.
Research Triangle Park, NC 27711

RFP NO1-CP-75899-69

Title: *Effect of dietary protein type and level on carcinogenesis*
Deadline: *July 26*

The objective of this project is to evaluate the effects of type of protein and level of protein on the induction and progression of spontaneous and chemically induced tumors in laboratory animals. This project will be coordinated with other Diet, Nutrition & Cancer Program projects investigating effects of various nutrients in carcinogenesis.

Contractors will be required to incorporate common procedures, such as animal handling procedures, dietary practices, and data processing, into the experimental protocol. Offerors will be required to discuss in the proposal the design of the experiment, dietary formulations, experimental methodologies for determining digestibility, anticipated problems, and proposed alternative designs. The final design will be specified by the Project Officer.

Contract Specialist: L.M. Waring
Carcinogenesis
301-427-7575

RFP NICHD-CEB-77-15

Title: *Case control study of the relative risk of malignant melanoma of the skin among women on contraceptive steroids*
Deadline: *Aug. 1*

Proposals are being sought to examine the relationship of contraceptive steroids to malignant melanoma of the skin in women using a classical case-control approach. Cases in this study should consist of women with malignant melanoma of the skin who

are in the reproductive age range and were therefore at risk of having been exposed to contraceptive steroids.

It is requested that written requests for this RFP include a mailing label to expedite shipment of the document.

NICHD
Office of Grants & Contracts
NIH, Landow Bldg
Room C-629
Bethesda, Md. 20014

RFP NO1-CP-75916-62

Title: *Data and information resources*
Deadline: *July 14*

NCI is interested in receiving two-year proposals to develop resources capable of responding to the development and analysis of components of activities described as data and information in content and scope.

Contract Specialist: D. Britton
Carcinogenesis
301-427-7575

SOURCES SOUGHT

RFP-NICHD-77-20

Title: *Cancer of the breast, endometrium and ovary with emphasis on the effects of oral contraceptives case control study*
Deadline for Resumes: *June 16*

Research is required to determine the relationship between oral contraceptive use and the risks of breast, endometrial and ovarian cancer. The case-control approach appears desirable in order to explore the relationships between oral contraceptive use and known and hypothesized risk factors for these tumors.

Specific issues which appear to be a particular importance are: 1. Oral contraceptive use prior to first pregnancy. 2. Oral contraceptive use in the presence of benign breast disease and other breast cancer risk factors (e.g., family history of breast cancer, etc.). 3. Prolonged "total use" of oral contraceptives. 4. Use of sequential vs. combination oral contraceptives. Data analysis would include estimation of the relative risk of breast, endometrial, and ovarian cancer among users of oral contraceptives as compared to nonusers. Analysis of the effects of potential confounding and interactive factors will be an important feature of the project.

It is anticipated that the study may require the ollaboration of a large number of hospitals in several etropolitan areas. A central data management center staffed by personnel knowledgeable in epidemiology and biostatistics appears necessary for successful coordination of the project and interpretation of the results.

A single contract award for phase I (Protocol Development and STudy Feasibility) would be made in Nov. 1977 for approximately one year. Phase II award for 2 years data collection and one year data analysis would follow in Nov. 1978. It is anticipated that phase II will be reactivated in subsequent years to maintain a continuing surveillance on the female population.

Interested organizations possessing the capabilities of performing such a project should submit four copies of resumes providing information on the following: 1. Prior epidemiological and biostatistical experience in designing and conducting large cooperative studies. 2. Professional qualifications of senior scientists and personnel specifically qualified and available. 3. Outline of previous projects including work previously performed or being performed in cancer epidemiology. 4. Description of general and specific facilities available for the anticipated work.

This is not a Request for Proposal. and responses should therefore not include cost or budget information. Concise responses directed specifically to the above items are requested. Responses will be evaluated and only those sources considered qualified for this project will be invited to submit proposals when the RFP is issued.

Contracts Management Section
National Institute of Child Health & Human Development
Landow Building, Room C-629
Bethesda, Md. 22014
Attn: R. Wagner

CONTRACT AWARDS

Title: Antibody-dependent cell-mediated cytotoxicity
Contractor: Sloan-Kettering Institute, $66,744.

Title: Adjuvant trials in resectable non-oat cell lung cancer
Contractor: UCLA, $374,137.

SOLE SOURCE NEGOTIATIONS

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

Title: Comprehensive cancer center communications network
Contractor: Illinois Cancer Council.

The Cancer Letter—*Editor* JERRY D. BOYD

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