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

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CARCINOGENESIS PROGRAM DIRECTION CHANGE NEAR FOR EXTRAMURAL RESEARCH; WORKSHOP TOPICS LISTED

NCI's Carcinogenesis Program is heading into a major restructuring of its $20 million-plus extramural research in which its status as essentially an extension of in-house research will be reformed into a program largely defined and developed by nongovernment scientists.

Gio Gori, deputy director of the Div. of Cancer Cause & Prevention and acting director of the Carcinogenesis Program, is following the

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In Brief

BEST GUESS ON NCI DIRECTOR: BROWN FIRST CHOICE, BENACERRAF SECOND; FDA ON SACCHARIN

BENNO SCHMIDT, chairman of the President's Cancer Panel and a member of the NCI director search committee, commenting on a report in one publication that the committee had recommended Ivan Bennett of NYU along with Arnold Brown of Mayo for the job: "That report should prove beyond doubt that no one on the search committee talked." Bennett was chairman of the committee, and although he may be qualified to run NCI, it isn't likely he would permit the committee to recommend him. Best guess at this point is that Brown was the committee's first choice, Baruj Benacerraf of Harvard its second. . . . **FDA'S SACCHARIN** proposal, banning it from prepared food and beverages but permitting its sale as a nonprescription drug, is open for comment until June 14. An informal hearing is scheduled for May 18-19. Send written comments to Hearing Clerk (HFC-20), FDA, Rm 4-65, 5600 Fishers Lane, Rockville, Md. 20857. The april 15 issue of the *Federal Register* which published the proposal included a history of saccharin use and tests and a description of the development of animal tests for carcinogens. . . . **NATIONAL CANCER** Advisory Board meeting May 23-24 will include presentations on NCI contracting procedures, the viral oncology research contract program, and an analysis of core support to centers. . . . **CLINICAL CANCER** center development will be discussed at the May 22 meeting of the NCAB Subcommittee on Centers & Construction. Also on the agenda are the intrainstitute committee's report and an analysis of the 10 largest center support grants. . . . **ALFRED KETCHAM**, Univ. of Miami and former NCI clinical director and chief of surgery, in the March/April issue of *Ca-A Cancer Journal for Clinicians:* "One must question the scientific basis of so much surgery performed today in an abortive manner, based on the assumption that remaining tumor will be controlled by other therapeutic modalities. Even more distressing is any undue delay in treatment associated with attempted 'conservative' tumor management with as yet unproven chemical or physical agents, only turning to conventional or potentially curable treatment when the tumor fails to respond. . . . The best way to avoid excessive surgery is to first perform adequate surgery."

CARCINOGENESIS COMMITTEE APPROVES WORKSHOPS FOR PRIORITY PLANNING

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pattern he established in developing the Diet & Nutrition Program, which he also heads.

Gori presented the newly chartered Carcinogenesis Scientific Advisory Committee with a list of proposed subjects for a series of workshops. Participants in the workshops will develop recommendations for individual research projects, to which the advisory committee will assign priority rankings.

The committee went along with most of Gori's workshop proposals and added a few more. Gori hopes the workshops can complete their task in time for submission of its recommendations to the committee for consideration at its July meeting. The workshop topics are:

—Metabolic and environmental markers of high risk populations.

—Assessment of current knowledge in structure and activity of carcinogens.

—Dose/response and potency determination in carcinogenesis.

—New predictive models of carcinogenesis for lung, breast, colon-rectum, pancreas, prostate and bladder.

—Dietary fat intake as a modulator of carcinogenesis.

—Metabolic modulation of carcinogen access to target cells and molecules, by age, sex, genetic polymorphism, diet, stress, toxicants and environment.

—Metabolic modulation of cancer expression after transformation, by the same categories as above.

—Roles of sex hormones and growth and stress hormones in carcinogenesis.

—Non-ionizing radiation carcinogenesis.

—DNA repair and carcinogenesis.

—Molecular mechanisms of transformation, including gene control, somatic mutation, epigenetic modes, and others.

—Biology of transformed cells, including membranes, proteins, nucleic acids, nutrition, respiration and catabolism.

—Metabolism of carcinogens, including aromatic hydrocarbons, nitrosamines, aromatic amines, inorganic carcinogens, and halogenated hydrocarbons.

—Anticarcinogens, including vitamin C, vitamin E, selenium, antioxidants, and retinoids.

—In vitro models of carcinogenesis, including neoplastic transformation of epithelial cells.

—Species response to carcinogens, including organotropism—molecular, cellular, tissue.

—Genetic and viral modulators of carcinogenesis.

—Modulation of immunocompetence and its effects on carcinogenesis, including immune surveillance.

Those topics were suggested by Gori and his staff, and the committee went along, although questioning the need for the study of viral modulators. Committee member Margaret Howell suggested that virologists already are doing a substantial amount of work in that field. Gori argued that "we can look at this with a different approach. . . . We don't operate in a vacuum. Sometimes we interface with others. That may be a moderate term. Step on toes may be more appropriate."

Workshop topics suggested by the committee were:

—Vaginal adenosis problems, related to DES.

—Two stage carcinogenesis.

—Differentiation in neoplasia.

—Biology of preneoplastic lesions.

Describing how the Program will now operate, a report prepared by Gori said:

"The extramural or collaborative Carcinogenesis Research Program (CRP) of NCI is organized to offer a targeted parallel alternative to unstructured grant-supported research, toward the definition of methods for the ultimate control of cancer. As such, the program will strive to balance the allocation of priorities and resources according to an assessment of national needs. The necessary choices will be determined by a mix of objective information, such as epidemiological realities and established scientific understanding, and of creative invention from the community of scientists.

"An overall plan of activities will utilize epidemiological clues of primary carcinogens and of those host and environmental factors that may influence host resistance or susceptibility. Epidemiologic and scientific knowledge would then help in selecting successful animal, man, or in vitro experimental models. In turn, investigations with these models would clarify the nature and mode of action of carcinogens and modifying factors, and would suggest methods for their elimination or control.

"The complexity of disciplines and scientific trends in contemporary carcinogenesis research indicates that many competent voices should be allowed to participate in the structuring of priorities at the national level. Towards such end, a new organization structure is proposed for the Carcinogenesis Program. The program director and his staff are responsible for the overall conduct of the operations and decision making. They are assisted by the Carcinogenesis Scientific Advisory Committee (CSAC), a group of expert peers from the scientific community that provide a balance of expertise in the definition of national priorities in carcinogenesis research. The CSAC will assist the program director and staff through the following cyclical process:

"A. The CSAC will define the most important and promising areas of carcinogenesis research.

"B. The program director and staff will convene workshops, on the topics identified by the CSAC, where scientific peer experts may discuss the opportunities for specific research projects and alternatives.

"C. The CSAC will consider the projects suggested by the workshops within the overall needs of a national carcinogenesis program, and will recommend

priorities for the execution of these projects.

"D. The program director and staff will relate these recommendations to NCI budget realities, and will coordinate with other agencies and programs in carcinogenesis research to avoid duplication and promote cross-fertilization of ideas; then those projects that can be funded by research contracts or by cancer research emphasis grants (CREGs) will be advertised nationally.

"E. The contract proposals and CREG applications received will be submitted by the program staff to scientific merit review by stnading committees of peers from the scientific community. Approved projects will be awarded by the program staff and project officers will be assigned.

"F. New data generated by the program, or by other research worldwide, will be monitored, submitted to, and reviewed by the CSAC and workshop attendees, to eventually modify existing priorities and to advance established understanding in carcinogenesis research.

"The dynamics of cancer research suggest that this review cycle could be renewed annually.

"Topical workshops will be attended by a small group of specialists meeting for one or two days. Attendees will receive considerable input from the program staff and enough introduction to insure productivity during the meeting. Twenty to 30 workshops are anticipated every year, allowing participation of 200 to 300 scientists. This process will generate research ideas from a cross-section of scientific expertise and opinion and hopefully may optimize the probability of advancing priority knowledge in carcinogenesis. It will also produce a backlong of desirable research projects to support requests for additional resources and funds, and to provide a realistic choice of top project priorities within the carcinogenesis program.

"Because the NCI project officers cannot be expected to encompass all the scientific competence necessary to monitor each project, they will be assisted in their task by expert consultants from the scientific community.

"The NCI Carcinogenesis Research Program has an intramural research component which will function independently of the extramural or collaborative program staff. Intramural scientists will conduct their own research and will participate in the structuring of the National Carcinogenesis Program much as outside scientists do; for instance, they may be attending workshops where their individual expertise is relevant, and will also serve as NCI project officers where their interest applies. The CSAC will also have the function of annual reviewing the scientific merit and program relevance of intramural research projects."

Much of the current carcinogenesis extramural research fits within the parameters of the proposed workshop topics. But Gori plans to establish a reserve of at least 20% to fund new projects. That reserve will be derived from contracts that are due to expire and from some cuts in ongoing projects.

"We won't make a flat percentage cut across the board," Gori said. Some existing contracts will not be touched, others will be cut in varying amounts, and some may be terminated.

New projects probably will not be funded with fiscal 1977 money, since most of that is already committed. Gori plans to have at least some of the projects ready for funding when FY 1978 money is available, after Sept. 30.

Some of the reprogrammed money may be awarded through Cancer Research Emphasis Grants. Those that appear to be more in the area of fundamental research will be advertised as CREGs.

NCI ADVISORY GROUPS TO BE REDUCED BY ONE-THIRD, WITH $800,000 CUTBACK

Drastic cuts in NCI advisory committees and review groups and a sharp reduction in their budget has been proposed to HEW following orders from the Carter Administration to curtail those operations throughout the federal government.

The NCI plan, drawn up hastily by Acting Director Guy Newell "without any outside advice and with very little from staff," calls for a reduction in committees from 43 to 26, and for trimming the number of individuals in the committee system from 621 to 413. Newell estimated these cuts would slice $800,000 a year from the cost of oeprating the committees, a cost that totalled $1.85 million in FY 1976.

The plan has been submitted to HEW Secretary Joseph Califano, whose approval is required to put it into effect.

Newell told the President's Cancer Panel last week that, two weeks ago, HEW had asked NIH to reduce the number and costs of its advisory committees. "Dr. (Donald) Fredrickson (NIH director) responded with a firm no," Newell said. "He pointed out the system is fragile as it is, and the workload already is overburdening. He defended NCI, very well I thought.

"Yesterday, however, we were told to reduce the number and costs. We were told to be imaginative, and were encouraged to try to experiment, to try to do the work of government with less advice."

Here's how Newell proposed to effect the cuts:

1. Several committees with contract review responsibilities had been split into two groups, committee A and committee B. This was to permit a committee member to respond to an RFP, in which case his proposal would be reviewed by the other committee. "Dr. Fredrickson said this was a luxury we couldn't afford," Newell said. Those committees will be combined, and the conflict of interest problem handled by forbidding an applicant from attending any part of a meeting in which his proposal is being reviewed.

2. Committees will be trimmed in size, with some

members not being replaced as their terms expire or when they resign.

3. Some committees that are called "advisory committees" but which are really "state of the art, workshop types," Newell said, will be terminated.

4. Some committees will be combined. For instance, the Breast Cancer Task Force includes four separate committees, all of which usually meet at the same time. They will be combined and the membership reduced by attrition.

5. The number of site visits, and the size of site visit teams will be reduced.

6. An effort will be made to arrange for site visitors to review more than one application when an institution has several under consideration.

"We view this as experimental," Newell said. "We will have to watch closely the quality of review and advice we get, and the workload."

Panel Chairman Benno Schmidt said he agreed "we can cut down, as long as we don't lose the value" of the system. "What we're getting is largely for free."

That isn't exactly the case. Committee members are paid $100 a day plus expenses for travel, hotel and meals. For meetings at NIH, daily expenses are limited to "actual and necessary" not to exceed $50.

Members of the Panel and the National Cancer Advisory Board receive $145 a day plus expenses.

The scientific community, which rarely is in total agreement on anything, is pretty much unified in the feeling that the success of NIH supported research depends on the peer review system. If the quality of that review is diminished, so will be the quality of research, scientists believe.

Growth in the number of committees in recent years can be attributed largely, at NCI at least, to the demand that contract proposals receive the same intensive review accorded grant applications, by non-government scientists. NCI has barely completed the task of chartering and manning its various contract review committees, and now must face the cutbacks before the system is fully implemented.

There are those who do not feel that the NIH peer review system is working all that well. Sidney Wolfe, director of Ralph Nader's Health Research Group, said he thinks more review ought to be done by NIH staff, with the help of a limited number of outside consultants.

The $1.85 million NCI spent on its committees did not include the cost of operating the NIH Div. of Research Grants study sections, which review most grants funded by NCI. The pressures to cut back presumably will also affect the study sections at a time when NCI has been lobbying for broader representation on those groups to improve review of clinical research and environmental carcinogenesis applications, among others.

Califano's office said that he was studying the NCI and NIH proposals but could not predict when his decision would be made.

CONTRACTS CHIEF OBJECTS TO CHARGE THAT NCI TRIED TO AVOID COMPETITION

James Graalman, chief of NCI's Research Contracts Branch, objected to the contention expressed in ***The Cancer Letter*** April 15 that NCI apparently "never had any intention" of competing the contract for carcinogenesis bioassay support services.

"We want to compete every contract we can," Graalman said. "We would like to compete this one. It just isn't fair to say that we didn't want to compete it."

The contract with Microbiological Associates expires June 30. NCI felt that there probably was no other organization qualified to handle the job and that the contract would have to be renewed as a sole source procurement. To determine if that were the case, the Carcinogenesis Section of the Research Contracts Branch published a "sources sought" announcement with a synopsis of the work to be performed in the government publication, *Commerce Business Daily*. If the announcement generated responses from organizations which appeared to be qualified, the contract would be competed and an RFP would be issued.

The announcement appeared in *CBD* April 1, and a deadline for submission of resumes was set for April 11. ***The Cancer Letter*** objected, contending that regulations required at least 15 days notice. Also, the announcement was not available to ***The Cancer Letter*** until too late to permit publication before the April 11 deadline.

Graalman said there is no regulation requiring the government to allow 15 days for responses after publication. "We try to do that when we can, but it isn't in the regulations," Graalman said. In some cases, sole source justification can be made with no publication at all. The reference to 15 days in the regulations is that the notice must be transmitted to *CBD* 15 days prior to the deadline; the actual publication date is not a consideration. In this case, the transmittal date was 15 days or more before April 11.

Graalman said that any responses received after April 11 would be considered in determining whether or not to go competitive.

Joe Federline, contracting officer for the project, said that a number of responses had been received and were being evaluated. A decision on whether or not to compete the contract will be made within a few days, he said.

MONOGRAPH TO INCLUDE PAPERS PRESENTED AT CONFERENCE ON ADJUVANT THERAPY

Adjuvant treatment of breast cancer accounted for one third of the papers presented at the International Conference on the Adjuvant Therapy of Cancer in Tucson last month. The conference was organized by the Section of Hematology & Oncology and the Univ. of Arizona College of Medicine Cancer Center, with

Sydney Salmon and Stephen Jones as cochairmen.

A monograph containing summaries of the papers will be published by Elsevier/North Holland Press. Abstracts of some of the papers follow:

ADJUVANT CHEMOTHERAPY OF OSTEOGENIC SARCOMA (OGS) – PROGRESS, PROBLEMS, PROSPECTS – Emil Frei and Norman Jaffe, Sidney Farber Cancer Institute

Following the demonstration that V-MTX-CF was effective in overt OGS, this program was applied as adjuvant to 34 consecutive patients between 1972 and 1975. No patient has relapsed after 20 months. By life table plot, 58% of 12 patients receiving MTX-CF and 70% of 22 patients receiving MTX-CF plus Adriamycin are disease free after 20 months. For all patients presenting with primary OGS at the Sidney Farber Cancer Institute since 1972, the survival by life table plot at 4 years is 80% as compared to 16% for the historical control group. The pharmacologic and cytokinetic rationale and interpretation of these results will be presented as a background for our third generation studies. This involves MTX q. wk. x 4 at the beginning, middle, and end of a 9-month program involving MTX-CF-adriamycin.

HYPERTHERMIA AS AN ADJUVANT TO RADIOTHERAPY AND CHEMOTHERAPY – Max Boone, William Connor, Thomas Cetas and John Leith, Univ. of Arizona College of Medicine

A growing body of biological evidence suggests that hyperthermia, either alone or in combination with ionizing radiation or anticancer drugs, may be a valuable adjuvant to cancer therapy. Temperatures in the range of 42°C to 45°C are directly cytotoxic, and cell lethality shows little or no dependence on levels of oxygenation. Such temperatures also inhibit recovery of cells from potentially lethal radiation or chemotherapeutic damage and from sublethal radiation damage. The interaction between hyperthermia and other anticancer agents may be due, in part, to different sensitivities as a function of stage of the cell cycle for the two agents.

We have examined the response of several normal tissues, including skin and spinal cord, to combinations of radiation, hyperthermia, and chemotherapeutic agents (e.g., adriamycin). It is evident that hyperthermia potentiates the effects of both ionizing radiation and adriamycin. The degree of potentiation achieved in experimental and spontaneous animal tumors is also under study.

The ultimate clinical success of localized hyperthermia will depend upon the use of effective methods to heat volumes of tissue to temperatures which are uniform and known absolutely to better than 0.5°C. In some circumstances, changes in temperatures of 0.5°C can alter cell survival by more than a factor of three.

ADJUVANT CHEMOTHERAPY WITH CMF IN BREAST CANCER WITH POSITIVE AXILLARY NODES – G. Bonadonna, A. Rossi, P. Valagussa, A. Banfi, U. Veronesi, Istituto Nazionale Tumori, Milan.

The CMF adjuvant program was started on June 1, 1973, with the intent to improve both disease-free period and survival in the high-risk group of operable patients (N+). Within 4 weeks from mastectomy, 386 patients were randomized to receive no further therapy or 12 intermittent monthly cycles of CMF. At 3 years from the beginning of study the actuarial analysis showed:

	CONTROL (%)	CMF (%)	P
FAILURE RATE	45.7	26.3	< 0.0001
Nodes 1-3	37.9	19.1	< 0.01
≥ 4	64.9	41.5	< 0.001
Premenopause	47.6	14.7	0.00001
Postmenopause	40.1	36.2	0.16
SURVIVAL RATE	78.6	89.6	0.08

The pattern of relapse was similar in both groups with preferential involvement of distant sites. Toxicity was moderate and reversible. No drug-induced neoplasm was observed. Present results confirm the efficacy of 12 CMF cycles in premenopausal patients. The decreased recurrence rate in postmenopausal women given CMF was appreciable only during the first 12 months. Postmenopausal women probably require a more intensive and prolonged adjuvant chemotherapy.

RISK-BENEFIT CONSIDERATIONS FOR ADJUVANT L-PAM CHEMOTHERAPY OF PATIENTS WITH BREAST CANCER AND NEGATIVE LYMPH NODES – A PRELIMINARY REPORT – Richard Bornstein, Stanley Levick, Leonard Levick, Kenneth Algazy, Mt. Sinai Hospital, Cleveland, and Albert Einstein Medical Center, Philadelphia

Recent data by Schabel has documented the efficacy of chemotherapy in the treatment of micrometastases. The beneficial effect of this approach has been proven in the treatment of osteogenic sarcomas in humans. Recent data by Fisher and Bonadonna have suggested the usefulness of this approach in the adjuvant treatment of women with breast cancer whose regional lymph nodes are positive at the time of surgery. These patients are the so-called "high-risk patients". However, examination of the NSABP data has shown that women with negative nodes have a 24% recurrence rate at ten years.

Because of this relatively poor prognosis even in patients whose regional nodes appear to be uninvolved, we have embarked upon a study of L-PAM given postoperatively to patients with negative nodes. To date 35 patients have been entered into the study and 22 are at least one year since starting therapy. There have been no recurrences to date nor have there been any significant toxic effects noted.

FEASIBILITY OF ADJUVANT CHEMOTHERAPY OF BREAST CANCER IN A PRIVATE PRACTICE SETTING – James Waisman, Clifford Ossorio, Robert Taub, Melvin Avedon, Michael Van-Scoy Mosher, Cedars-Sinai Medical Center, Los Angeles

Thirty-nine patients with cancer limited to the breast and axilla (37 stage IIa, 2 stage III) received cyclophosphamide p.o D1-14, methotrexate i.v. D1&8, and 5-FU i.v. D1&8, with the course repeated q 28 days. Attempts were made to reduce the gastrointestinal, mucous membrane, and bone marrow toxicity described in Bonadonna's series (New Engl. J. Med., Feb. 1976, pp. 405-09) by using approximately 2/3 of Bonadonna's dose schedule.

All patients had modified radical mastectomies and 3 had postoperative radiation therapy. The median age was 55 with a mean period of 12 months on therapy. There are 26 post- and 13 premenopausal patients in this series.

Most patients had only mild nausea, rarely associated with vomiting. Three of 39 had stomatitis. There was one episode of hemorrhagic cystitis. No patient had clinically significant bone marrow suppression. Most patients started on CMF were switched to alkeran, methotrexate, and 5-FU (AMF) and 2 other patients were initiated on AMF, all because of an inordinate fear of alopecia.

Adjuvant chemotherapy with CMF for breast cancer is well-suited for use in private practice in respect to tolerable toxicity, efficacy, and maintenance of near-normal functioning.

TRIPLE THERAPY AS AN ADJUVANT TO TESTICULAR CANCER SURGERY – Fred Ansfield and Guillermo Ramirez, Univ. of Wisconsin

The potent antitumor action of actinomycin D, chlorambucil, and methotrexate in testicular cancers other than seminoma was observed in 35 of 44 patients (80%) who had demonstrable distant dissemination and achieved a 50% to complete regression. There were no drug-related deaths in this series. These factors, coupled with the reports of significant mortality from testicular tumors whether lymphadenectomy revealed positive or negative nodes, prompted us, beginning 12 years ago, to treat aggressively all malignant testicular tumors other than seminoma with triple therapy as an adjuvant to orchiectomy, whether or not a node dissection had been performed. Chemotherapy was not delayed in patients referred to us who did not have a lymphadenectomy, as postponing triple therapy may outweigh any benefit that might accrue from this extensive surgical procedure. Aggressive triple therapy as an adjuvant to surgery was given to 32 patients, 4 of whose cell type was choriocarcinoma (all 4 living N.E.D. 4-12 years), 17 embryonal (10 living N.E.D. 3-11 years), and 11 teratocarcinoma (10 living N.E.D. 3-11 years). These results (75% living N.E.D. more than 3 years) are significantly better than those obtained in the 44 patients with disseminated cancer (6 living N.E.D. 2-14 years, 14%).

Radiotherapy was not employed in the group that received the adjuvant therapy or in those with disseminated testicular cancer.

ADJUVANT RADIOTHERAPY FOR CARCINOMA OF THE SIGMOID COLON AND RECTUM – Marvin Romsdahl and Hubert Withers, Univ. of Texas System Cancer Center

Approximately 70% of colorectal carcinomas occur in the distal sigmoid and rectum, and since the local recurrence rate for lesions below the peritoneal reflection ranges from 20-35% following surgery, a program of postoperative radiotherapy is now being evaluated for its effect on local control. Patients with lesions which penetrate the entire bowel wall and/or those having regionally involved nodes receive radiotherapy (~5000 rads) over a period of ~6 weeks commencing 3-8 weeks after a curative operation. Forty-five patients treated in this manner have been compared with 168 patients treated without adjunctive radiotherapy. Two local recurrences have occurred in the group receiving radiotherapy, which represents a substantially reduced incidence compared to the latter group. Complications attributable to radiotherapy developed in 5 patients and include bowel obstruction and proctitis. A regimen of radiotherapy commensurate with minimal complications has been determined and surgical measures to facilitate this therapeutic approach have been identified. This experience strongly suggests that surgery followed by adjuvant radiotherapy may be carried out with a reasonable complication rate and is effective in reducing local recurrence of rectosigmoid carcinoma.

ADJUVANT CHEMOTHERAPY IN OSTEOSARCOMA OF ADULTS – W.K. Murphy, R.S. Benjamin, and J.A. Gottlieb, Southwest Oncology Group, M.D. Anderson Hospital

Although survival figures vary, approximately 70%-90% of patients having surgery for primary osteosarcoma die of distant metastases. In 1971, after adriamycin (Adr) had been found to have activity in metastatic osteosarcoma, an adjuvant chemotherapy pilot study was initiated for osteosarcoma utilizing Adr 50 mg/m2, IV once every 21 days for 10 courses. A total of 6 patients were entered. All patients relapsed, the intervals to relapse being 2,6,8,11 and 14 months.

In view of the obvious failure of this program and in view of demonstrated efficacy of the combination, another adjuvant study was initiated utilizing vincristine 2 mg/m2 IV weekly for 6 weeks, then d-1 of each course; Adr 40 mg/m2 d-2 IV; Cyclophosphamide 400 mg/m2 d-2 IV; and DTIC 200 mg/m2/dx5d. The DTIC was given for 4 courses only. Courses were repeated at 3-week intervals and at a total dose of 450 mg/m2 of Adr, all chemotherapy was stopped. A total of 19 patients have been entered on study (9 in pilot and 10 on formal protocol). One patient is inevaluable because of multiple protocol violations. Of the 18 evaluable patients, 5 patients have relapsed (at 2,3,12,15, and 26 months) and 13 patients remain disease-free (at 7,12,14,14,16, 16,19,24,25,28,30, and 36 months). Toxicity for patients entered on this adjuvant "CYVADIC" protocol has been mild to moderate with no serious therapy-related complications. The disease-free survival is 72% at this time, compares favorably with any other adjuvant therapy program and is significantly superior to our own historical controls.

Other papers presented at the conference were:

THE RATIONALE FOR ADJUVANT THERAPY OF CANCER– Kinetic rationale for adjuvant chemotherapy for micrometastases–S. Salmon; Experimental basis for adjuvant therapy–F. Schabel; Rationale and experimental basis for immunotherapy–G. Mathe; Immunotherapy of cancer–An overview–E. Hersh.

BREAST CANCER – Studies of the Primary Breast Cancer Therapy Group–B. Fisher; Ovarian irradiation and prednisone following surgery and radiotherapy for carcinoma of the breast–J.W. Meakin; Adjuvant chemotherapy-radiotherapy in breast carcinoma–G. Ramirez; The effect of adjuvant chemotherapy on endocrine function in patients with operable breast cancer–R. Rubens, R. Bulbrook, R. Knight, J. Hayward, H. Bush, D. George, D. Crowther, R. Sellwood; Adjuvant chemotherapy with melphalan (P), methotrexate (M), and 5-fluorouracil in breast cancer–S. Desai, S. Taylor IV, J. Merrill, A. Bianco, H. Goldsweig, T. Kisielus, J. Phillip, W. DeWys; L-PAM versus combination chemotherapy in the management of primary breast cancer–A. Lipton, W. Demuth, R. Dixon, R. Gottlieb, R. Kane, M. Kukrika, R. Moquin, D. Nahrwold, J. Ricci, W. Shaver, S. Ward, D. White, H. Harvey; Adjuvant therapy of breast cancer with adriamycin/cyclophosphamide–N. Hammond, S. Jones, S. Salmon, R. Miller, R. Heusinkveld; Adjuvant chemoimmunotherapy following regional therapy in breast cancer–A. Buzdar, G. Blumenschein, J. Gutterman, C. Tashima, G. Hortobagyi, W. Wheeler, E. Freireich; Adjuvant chemotherapy of node-positive breast cancer in the community–J. Carpenter, W. Maddox, H. Laws, D. Wirtschafter, J. Durant, S. Soong; Adjuvant radiotherapy and chemotherapy in stage II carcinoma of the breast–H. Abu-Zahra, B. McDonald, J. Maus, G. Mok, S. Yoshida; MER chemoimmunotherapy of stage II breast carcinoma–M. Perloff, J. Holland, G. Lesnick, J. Bekesi; Adjuvant chemotherapy and chemoimmunotherapy for breast cancer–F. Sparks, K. Ramming. R. Wolk, M. Goldsmith, M. Dollinger, D. Morton; Adjuvant chemoimmunotherapy of stage IV (NED) breast cancer–G. Blumenschein, A. Buzdar, C. Tashima, G. Hortobagyi, J. Gutterman.

GENITOURINARY, GYNECOLOGIC, AND GASTROINTESTINAL TUMORS – Multimodal therapy of testicular tumors–M. Peckham; Role of preoperative radiation therapy in endometrial carcinoma–A. Sudarsanam, K. Charyulu, B. Hintz; Adjuvant immunotherapy of ovarian cancer: A preliminary report–D. Alberts; Pilot study of gastric cancer with adjuvant chemotherapy–H. Lerner; Chemoprophylaxis for patients with colorectal cancer–M. Li and S. Ross; Adjuvant therapy with 5-FU after surgical resection of colo-rectal cancer–T. Grage, for the Central Oncology Group; Adjuvant chemotherapy and chemoimmunotherapy for locally advanced large bowel adenocarcinoma: Preliminary report of a SWOG study–F. Panettiere; Systemic adjuvant immunotherapy and chemoimmunotherapy in patients with colorectal cancer (Dukes' C class): Prolongation of disease-free interval and survival–G. Mavligit, J. Gutterman, M. Malahy, M. Burgess, C. McBride, A. Jubert, E. Hersh.

MELANOMA AND SOFT TISSUE SARCOMA – Adjuvant therapy in melanoma and sarcomas–Donald L. Morton and F.R. Eilber; Transfer factor (TF) immunotherapy in stage II malignant melanoma–R. Bukowski, S. Deodhar, J. Hewlett; Immunotherapy of melanoma with 2-4 dinitrochlorobenzene (DNCB)–S. Mansour; Malignant melanoma: A pilot study of adjuvant chemoimmunotherapy–A. Paterson, T. McPherson; Adjuvant therapy of osteosarcoma with adriamycin–J. Holland; Effects of adriamycin (ADM) in the adjuvant treatment of osteosarcoma–M. Gasparini, F. Fossati-Bellani, L. Gennari, G. Bonadonna.

PEDIATRIC NEOPLASMS – Adjuvant therapy in Wilms' tumor, rhabdomyosarcoma, osteosarcoma, and other neoplasms: An overview–W. Sutow; Primary chemotherapy in the management of pelvic rhabdomyosarcoma in infancy and early childhood–D. Hays and J. Ortega; Adriamycin, cytoxan, and vincristine in the adjuvant treatment of localized Ewing's sarcoma–F. Fossati-Bellani, S. Barni, M. Gasparini. A. Luttuada, G. Bonadonna.

LUNG CARCINOMA – Combined modality approaches in lung cancer–R. Livingston; Regional immunotherapy using intrapleural BCG and isoniazid for resectable lung cancer–M. McKneally and C. Maver; Immunotherapy of resectable squamous cell carcinoma of the bronchus (stage I and II)–P. Pouillart, G. Mathe, T. Palangie, P. Huguenin, P. Morin, H. Gautier, A. Baron, A. Ledederte; Immunotherapy of lung cancer–P. Wright, L. Hill, R. Anderson, S. Hammar; The role of adjuvant radiation therapy in stage III and IV oat cell carcinoma of the lung–C. Williams, M. Alexander, E. Glatstein, J. Daniels; Immunotherapy for advanced lung cancer–R. Crispen, S. Warren; Treatment of small cell carcinoma of the lung with cyclophosphamide, adriamycin, and VP12-213 with or without MER–J. Aisner, R. Esterhay Jr., P. Wiernik.

HEAD & NECK, THYROID, BRAIN TUMORS, COMPLICATIONS OF ADJUVANT THERAPY – Methotrexate-Leucovorin with immunotherapy as adjuvant to surgery and radiotherapy in stage III-IV head and neck squamous cancer patients–S. Taylor, IV, D. Bytell, G. Sisson, S. Nisius, W. DeWys; High dose methotrexate-citrovorum as initial adjuvant therapy in a multimodality approach to advanced squamous cell carcinoma of the head and neck: A pilot study–S. Pitman, D. Miller, R. Weichselbaum, E. Frei III; Multimodality treatment for high risk thyroid carcinoma–B. Durie, D. Hellman, R. O'Mara, J. Woolfenden, M. Kartchner, S. Salmon; Combination chemotherapy and split course radiotherapy in malignant glioma of the brain–H. Gilbert, L. Sadoff, D. Eder, A. Kagan, H. Nussbaum, P. Chan, A. Rao; Adjuvant chemoimmunotherapy in central nervous system tumors: A preliminary report–S. DeCarvalho, A. Kaufman, A. Pineda; Second malignancies following

initial breast cancer in prelonged thio-tepa adjuvant chemotherapy—P. Chan, L. Sadoff, J. Winkley.

HEMATOLOGIC MALIGNANCIES – Combined modality treatment of lymphomas, including Hodgkin's Disease—S. Rosenberg; Long term results of a controlled clinical trial on the sequence radiotherapy-chemotherapy in clinical stages I and II of Hodgkin's disease—Radiotherapy-Chemotherapy Group of EORTC—G. Mathe and M. Tubiana; Chemotherapy (MOPP) and total nodal radiotherapy in pathological stage IIB, IIIA and B Hodgkin's Disease—C. Coltman, E. Montague, C. Haskins, T. Moon; Adjuvant chemotherapy with CVP after radiotherapy in stage I-II non-Hodgkin's lymphomas—A. Lattuada, G. Bonadonna, A. Banfi, P. Valagussa, S. Monfardini; Combined modality treatment in the malignant lymphomas—E. Glatstein, S. Rosenberg, H. Kaplan; Chemotherapy vs. chemoimmunotherapy in non-Hodgkin's lymphomas—S. Jones and S. Salmon; Adjunctive immunotherapy of patients with mycosis fungoides—Z. Olkowski, J. McLaren, P. McGinley, F. Bilek; Comparison of the results of two acute lymphoid leukemia protocols: One with a nine-month, and one with a 25-month, pre-immunotherapy-chemotherapy—G. Mathe, L. Schwarzenberg, F. de Vassal, M. Delgado, J. Pena-Angulo, D. Belpomme, P. Pouillart, D. Machover, J. Misset, J. Pico, C. Jasmin, M. Hayat, M. Schnider, A. Cattan, J. Amiel, M. Musset, C. Rosenfeld; Combined modality management in acute leukemia—J. Holland.

ADJUVANT THERAPY OF CANCER – GENERAL COMMENTS – Ongoing adjuvant clinical trials in solid tumors—A. Louie, S. Mikulski, D. Von Hoff, M. Rozencweig, F. Muggia; The correlation of chemotherapy activity in advanced disease with results in adjuvant study—S. Carter; Adjuvant therapy of cancer: An overview—V. DeVita.

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 NO1-CP-75913-50

Title: *Studies in colon carcinogenesis in organ culture of intestinal mucosa*
Deadline: *June 3*

The basic objective of this project is the development of new or improved methods for organ culture of the intestinal mucosa, especially in systems in which it will eventually be possible to study agents and mechanisms involved in carcinogenesis and anti-carcinogenesis.

The main thrust of the current project is to define the best conditions for maintenance of normal structure and function of the intestinal mucosa in organ culture, to investigate whether such cultures can undergo true malignant transformation in vitro by appropriate treatment, to perform similar investigation in explant cultures in intact animals, and to perform metabolic and long-term carcinogenesis experiments.

It is expected that a doctoral level person or one with equivalent experience with working knowledge in chemical carcinogenesis research cell biology and biochemistry will act as project leader.

Contract Specialist: Joseph McHugh
Cause & Prevention
301-427-7957

RFP NO1-CP-75912-50

Title: *Studies of metabolic capacity in intestinal mucosa*
Deadline: *June 3*

The objective of this project is to study the metabolic capacity of the intestinal mucosa itself, with regard to the production of potential colonic carcinogens, mutagens and teratogens from exogenous and/or endogenous known or suspect colonic precarcinogens, carcinogens and promoters.

The contractor will be required to conduct studies to evaluate the metabolic capacity of intestinal mucosa in the colonic carcinogenic process. The studies are designed to determine the relationship of intestinal epithelial cells to the metabolic processes involved in colonic tumorigenesis. It is expected that a doctoral loevel person or one with equivalent experience with a working knowledge in chemical carcinogenesis research, cell biology and biochemistry will act as project leader.

Contract Specialist: Joseph McHugh
Cause & Prevention
301-427-7957

RFP NO1-CP-75911-56

Title: *Synthesis of radioactive retinoids for metabolic and pharmacologic studies relating to prevention of lung cancer and other epithelial cancers*
Deadline: *June 3*

NCI is interested in establishing a contract for this purpose. The basic objective of this contract is the synthesis of radioactive retinoids for use as tracers in metabolic studies both in vivo and in vitro. The approach will involve the synthesis of small quantities of several different retinoids, the choice of which will be dictated by the needs and interests of the Carcinogenesis Program.

Proposed compounds might include modifications of the ring, side chain, or terminus of the retinoid molecule with variations in both the radioactive isotope (^{14}C or ^{3}H) and the position of label incorporation.

A five-year or greater effort is anticipated in the effective pursuit of this project. However, any contracts resulting from this RFP will be written for a three-year period. The estimated cost range for the

three-year period is $210,000-$285,000.
Contract Specialist: Melvin Hamilton
Cause & Prevention
301-427-7575

RFP 210-77-0136-0000

Title: *Cutting oils and nitrosomines-carcinogenesis*
Deadline: *June 10, approximately*

The National Institute for Occupational Safety & Health is soliciting proposals from organizations interested in determining the potential of cutting oils containing nitrosomines to produce tumors both topically and systematically when applied topically to the skin.

Contracting Officer: M. Stitely
NIOSH
Rm 1-58
5600 Fishers Lane
Rockville, Md. 20857

CONTRACT AWARDS

Title: Technical support services for the ICRDB Program
Contractor: Franklin Institute, $61,503.

Title: Role of circulating tumor antigens
Contractor: Scripps Clinic & Research Foundation, $130,588.

Title: Adjuvant trials in resectable non-oat cell lung cancer
Contractor: Fred Hutchinson Cancer Research Center, $331,311.

Title: Continuation of a contract, Mammary gland responsiveness to multiple hormones
Contractor: Univ. of North Carolina, $95,000.

Title: Continuation of a contract, Study effects of nucleic acid preparations on the biological properties of mammary carcinomas
Contractor: Baylor College of Medicine, $95,000.

Title: Continuation of a contract, Study of role of stroma in the growth of neoplastic and pre-neoplastic lesions of the mammary gland
Contractor: Stanford Univ., $95,000.

Title: Continuation of a contract, Prolactin interactions in mammary gland cells
Contractor: Univ. of Kansas, $91,300.

Title: Chemical carcinogenesis and immunity
Contractor: Public Health Research Institute, New York City, $79,433.

Title: Development of H-2 recombinant and mutant strains
Contractor: Washington Univ., $72,804.

Title: Breast Cancer Detection Demonstration Project
Contractor: Samuel Merritt Hospital, Oakland, $287,391.

Title: Continuation of an ongoing contract, Mammary cell cultivation
Contractor: Pennsylvania State Univ., $68,600.

Title: Survey of the Journal of the NCI readers, subscribers and authors
Contractor: King Research Inc., Rockville, Md., $56,614.

Title: Chemoimmunotherapy of acute myelocytic leukemia
Contractor: Mt. Sinai School of Medicine, $210,631.

Title: Community Based Cancer Control Program – phase II – implementation
Contractor: Long Island Cancer Council, $6,522,900.

SOLE SOURCE NEGOTIATIONS

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

Title: Housing and maintenance of a chimpanzee breeding colony
Contractor: Southwest Foundation for Research & Education.

Title: Technical support services of the Systems Planning Branch, OPPA/OD, NCI
Contractor: Mitre Corp.

Title: Study of glycoproteins of the mammary cell surface
Contractor: The Wistar Institute.

Title: Evaluation of serum LDH isoenzymes in women with breast tumors
Contractor: Mercy Hospital & Medical Center, Chicago.

Title: Comparative study of xeromammography versus film mammography
Contractor: Stella & Charles Guttman Breast Diagnostic Institute.

Title: Biological characterization studies of animal mammary tumors
Contractor: Mason Research Institute.

Title: Studies on therapy of patients with stage II and stage III carcinoma of the breast
Contractor: Evanston Hospital.

Title: Pathological history of the mammary gland in pseudohermaphroditic rats and mice
Contractor: City of Hope Medical Center.

The Cancer Letter—*Editor* JERRY D. BOYD

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