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L-PAM, LESS THAN RADICAL SURGERY RESULTS HOLDING UP; NEW BREAST CANCER STUDIES SOUGHT

The encouraging results on use of adjuvant chemotherapy for breast cancer patients, reported a year ago this month by Bernard Fisher and his colleagues in the National Surgical Adjuvant Breast Project, are still holding up, Fisher told the Breast Cancer Treatment Committee this week.

Fisher said that premenopausal patients receiving L-phenylalanine mustard (L-PAM) continue to have a five-fold improvement in recurrence over the group which received a placebo. In postmenopausal patients, the improvement is two-fold.

The results of the study reported last year comparing radical and total mastectomy are also holding up, Fisher said. There is essentially

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In Brief

FREIREICH ON NUTRITION: DIET CAN AFFECT IMMUNE SYSTEM, EFFECTIVENESS OF CANCER DRUGS

EMIL FREIREICH, M.D. Anderson, on nutrition and its relationship to cancer and cancer treatment: "Nutritionally deficient diets are immunosuppressive. There are also specific dietary deficiencies which affect specific components of the immune system. This almost certainly plays an important role in the host defense against not only the cancer but on the infectious complications that frequently complicate therapy. . . . Studies of essential nutrient reserves in patients with chronic debilitative disease such as cancer reveal that there are specific deficiencies in virtually every area. For instance, deficiency of folic acid, vitamin C and the B vitamins has been widely reported in such patients. These specific essential nutrient deficiencies interact specifically with drugs which affect those sites. For instance, methotrexate effectiveness, both on the normal tissue and on the tumor, is significantly affected by the body stores of folate. . . . Drug metabolizing enzymes of the liver are susceptible to inhibition by inadequate nutrition. Thus, for many drugs, where the rate of degradation is affected by drug metabolizing enzymes, a dramatic change in the effectiveness of such treatment would result from alterations in the nutritional status of the host." . . . **NEW ORGANIZATION**, the Oncology Nursing Society, is offering charter membership to RNs until Oct. 1. The society hopes to further efforts to generate new knowledge applicable to the care of persons with cancer, transmit that knowledge to nurses and others involved in the prevention of cancer and care of persons with the disease, encourage communication with others studying the malignant processes in man, and promote education experiences for those interested in oncology nursing. Send $20 charter fee to the president of the Society, Lisa Marino, 528 River Oaks Dr., River Forest, Ill. 60305. Marino is oncology nurse coordinator at the Univ. of Chicago.

FISHER SAYS ADJUVANT CHEMOTHERAPY MAY BE READY FOR PRACTICE IN A YEAR

(Continued from page 1)

no difference in recurrence rates between the two procedures, he said.

The prospect of such vastly improved treatment received national publicity because the wives of both the President and Vice President underwent mastectomies. Patients have been demanding chemotherapy, although as Fisher notes, it is still a research program.

There are some who insist that NCI should move immediately to get the L-PAM following surgery regimen into general practice at least for patients with positive axillary nodes. Others contend it will be years before the long term effects are known of L-PAM and other drugs being tested in similar studies, and that general use should be discouraged for now.

Fisher was reluctant to put any time schedule on when some form of adjuvant chemotherapy would be ready for general use against breast cancer. But he is adamant about not waiting for long-term toxicity results. "There's a trade off, and when you're worrying about only some relatively minor side effects, it would be silly to wait 10 years," Fisher told ***The Cancer Letter.***

Pressed for an estimate, Fisher said it is possible that a regimen could be ready for general practice within a year.

"The problem then won't be with patients," Fisher said. "When you point out improved survival chances, patients will accept chemotherapy. The big problem will be selling it to the physicians."

Fisher's report to the Treatment Committee, one of eight by Breast Cancer Task Force contractors, included these points:

- The study comparing total mastectomy alone vs. total mastectomy plus radiation vs. radical mastectomy alone for patients with clinically negative nodes is in its fifth year, with 1,760 patients. For patients with positive nodes, the study compares total mastectomy plus radiation vs. radical mastectomy alone. There are still no differences in recurrence.
- The NSABP stopped entry in the L-PAM protocol last February and started a new study comparing L-PAM with 5-Fluorouracil (5-FU) with 300 patients, about half in each group. There has been no recurrence in either group.
- The group soon will propose a segmental mastectomy protocol. "Whether it can be accomplished in the United States is problematic," Fisher said. "The question is whether enough physicians and patients would accept the risk. I think we might go ahead and propose it, and if we can't get it started then take an ad in the New York Times and say, 'Well, we tried, but it can't be done here. Maybe in some other country.'"

Fisher said the study would have as a control total mastectomy plus axillary dissection, compared with segmental mastectomy plus axillary dissection and segmental mastectomy plus axillary dissection plus breast radiation. The nodal status must be known, and there would be some positives and some negatives in each. Those with positive nodes would receive the same chemotherapy across the board. If there is recurrence in the breast, the patient would then get a total mastectomy.

"It will be difficult for some women to make the decision, on or off," Fisher said. "Some will be willing to try, some won't want to take the chance, some who will leave it up to their physicians. I do believe there is a significant number of women who want this, provided their doctors present it to them fairly."

- The fact that 25% of patients with negative nodes have recurrence within 10 years justifies studies to develop methods to prevent recurrence.

David Ahmann, Mayo, reported on his study in which patients with positive nodes, following modified radical mastectomy, received one of four drug regimens and/or radiotherapy.

Ahmann said that the study first included a control group which received no further treatment after surgery. But after the findings reported by Fisher last year, the control group was discontinued, for ethical reasons. Before it was dropped, eight patients had been admitted to the control group and there were three recurrences within 44 weeks.

Ahmann has had 13 patients receiving L-PAM from eight to 35 weeks, with no recurrences; five receiving radiotherapy alone from 38 to 91 weeks, with no recurrences; 21 receiving a three-drug combination of 5-FU, cyclophosphamide and prednisone for more than 50 weeks, with five recurrences; and 20 receiving the same drugs plus radiotherapy for 60 weeks, with one recurrence.

Ahmann said toxic effects include mild immunosuppression with L-PAM, some nausea with the three drugs, and a somewhat greater degree of nausea with the drugs plus radiation, although there have been no serious problems.

Ahmann said he was not convinced the chemotherapy will change survival rates. "I would be ethically comfortable continuing the controls. But it became difficult, with the publicity last fall. Patients were asking about it, demanding further treatment, although many still say they don't want any additional therapy.

Paul Carbone, chairman of the Treatment Committee, pointed out that the Mayo study was the only one that includes chemotherapy plus radiotherapy.

Edward Scanlon, of Evanston, Ill., Hospital (Northwestern), reported on his study that is identical to Mayo's except that it substitutes BCG for radiotherapy. His program began last July 1, and he said they have had difficulty finding enough eligible patients.

Of 224 breast cancer patients at the hospital since

January, only 12 have been put on the protocol. Only 22% had positive nodes, and of those entering the hospital since July 1, only 18% had positive nodes.

Scanlon said he agreed there should be no control group. "It's impossible to tell patients they might not get treatment. There's no chance with the atmosphere we have today that you can sell a program that includes no treatment for some."

Charles Hubay, Case Western Reserve, said he has experience problems getting people into his study "owing to organizational growing pains, changes in staging patterns and patient resistance."

Hubay also noted the impact of breast cancer publicity last year. "Since this study was initiated in the fall of 1974, when wide-spread publicity was given to two breast cancer patients, an increased number of patients were seen with early breast cancer without nodal involvement. Our own experience pattern in 295 patients over a 15-year period revealed that 50% of patients had negative nodes and 31% had three or more positive nodes.

"In the first four months of our study, 60% had no positive nodes and only 13% had three or more positive nodes. An excellent trend toward early diagnosis and therapy, but limiting the candidates for study."

Hubay said that, as awareness has waned, patients are starting to come in a little later, with a subsequent increase in nodal involvement.

The purpose of Hubay's study is to assess the early combination of surgery, endocrine therapy, chemotherapy and immunotherapy in a carefully planned, sequential regimen, for its effect on the potential for possible cure or prolonged survival in patients with stage II and stage III breast cancer.

Hubay said, "Following surgery, at a time when the tumor burden is low, breast cancer cells beyond the confines of the operative site could theoretically be attacked while small in number and clonal development abrogated. It is conceded generally that large metastatic tumor masses have the propensity of resisting host immunological defense mechanisms, and likewise, effective chemotherapy is uncertain.

"The presence of estrogen-binding protein or estrogen receptors in breast cancer tissue now appears to be a method of selecting patients with hormone dependent tumors as shown by Brodkey, Jenson, McGuire, Pearson and others. We have been studying breast cancers for the presence of estrogen receptors, although its presence or absence in breast cancer tissue is not the basis for treatment in our study.

"Our protocol involves the study of primary operable breast cancer patients seen in three Cleveland hospitals involved in the study. The patients will receive early postoperative therapy, after being classified in the unfavorable stage II or III with positive nodes in the axilla. Because of the low number of patients with positive nodes seen, we recently modified the study to include patients with one or more positive nodes.

"After clinical evaluation, a modified or conventional radical mastectomy is performed on all suitable patients. After wound healing has been completed, pathologic data obtained for staging and estrogen receptors measured, eligible patients are given the opportunity to participate in the study. Informed consent is obtained. The estrogen binding protein positive or negative stage II patients form two basic study groups.

"One of the criteria for entering the study is that the tumor tissue must be analyzed for the presence or absence of estrogen receptors by McGuire. . . . Initially for the first several months of the study, we put the favorable patients in one group (stage I) including those who axillary nodes were negative or in whom one to three adjacent nodes were positive. In this group we expect a 75-85% five-year survival. Estrogen receptors were determined in as many patients as possible. No therapy is given and we are following these patients. . . .

"The unfavorable patients, initially the patients with four or more, but now one or more positive axillary nodes, were divided into two groups, those with estrogen receptors being present and those with estrogen receptors being absent or low. These were randomized into 3 sub-groups, one group receiving no therapy (control group), another group receiving chemotherapy and the anti-estrogen drug for one year, and a third group receiving chemotherapy and the anti-estrogen drug for one year, followed by immunotherapy for one year.

"We believe that this study will allow correlation of the presence or absence of estrogen-binding protein or other tumor markers in primary breast cancer with the timing of subsequent therapy in patients with a poor prognosis.

"The end-point of the study will be the first evidence of treatment failure, that is, the presence of tumor in local, regional or distant sites confirmed by biopsy or other evidence by clinical, radiologic or radio-isotopic methods. Patients assigned to the control group do not receive treatment, but are followed every three months with appropriate physical examinations, x-rays and laboratory determinations.

"Patients assigned to a chemotherapy group receive treatment no sooner than two weeks and no later than six weeks following surgery. The following regimen is used: 5-FU 400 mg/M^2 given intravenously on days 1 and 8, methotrexate 25 mg/M^2 given intravenously on days 1 and 8, cytoxan 60 mg/M^2 orally in two divided doses for 14 days and the anti-estrogen drug, tamoxifen, is given as 20 mg. doses twice daily for one year. The estrogen inhibitor, tamoxifen, has been studied in Europe by Tagnon and others, who have reported a 35% remission rate in pre- and post-menopausal women with metastatic disease. It apparently works as a competitive inhibitor to the binding of estrogens by tumor tissue.

"The chemotherapy cycle is repeated every month for 12 treatment courses. At the present time we are not at the one-year level for the first patient and we have not yet started immunotherapy with BCG at this time, but our first patient is coming up for BCG therapy in October. We hope to glean information from this conference and from others the preferred method.

"Clinical evaluation is done frequently in patients on the chemotherapeutic drugs and toxicity is noted with hematologic and blood chemical determinations for bone marrow, renal, and gastrointestinal toxicity. The usual criteria for dose modifications are followed.

"To the present, all patients have tolerated the chemotherapy and have not required significant alterations in therapy because of toxicity. A number of other parameters are being studied, including lymphocyte testing for antitumor immunity, a battery of skin test antigens, including mumps, candida, PPD, dermatophytin, streptokinase-streptodornase, determined every three months, as well as bone surveys and bone scans. While on protocol the patient is followed carefully by oncologists and evaluations made of performance scale and possible recurrence. Repeat tests of lymphocytes and sera are carried out for antitumor immunity."

Arnold Powell, Hubay's colleague at Case, reported on his immunosurveillance project, which he described as applying immunology techniques to the detection of tumors in general and breast cancer in particular.

Frank Sparks, UCLA, discussed his study in which patients received either radical mastectomy or modified radical mastectomy plus radiotherapy, then are divided into two groups—one getting the drug combination of cyclophosphamide, methotrexate and 5-FU plus BCG; the other, the same drugs plus BCG plus tumor cell vaccine.

Most of the patients do not receive radiotherapy, Sparks said. He feels it may make them less able to handle aggressive chemotherapy.

Twenty patients have received the drug plus BCG therapy for two to 55 weeks, with no recurrence. Fourteen patients have received the drug-BCG-TCV treatment for six to 60 weeks, also without recurrence.

Sparks said he was pleased by the progress so far, but he questions whether or not patients will continue for the full 19 cycles required by the program. "They have to come in every week and face their cancers," he said. "That's very hard on them emotionally. This program seems to produce more anxiety among the nurses, who identify with the patients."

Carbone summarized the discussion by suggesting projects he feels should be undertaken next.

"We've asked for the development of therapy for patients with positive nodes, using one agent, two agents, or more, by themselves, or with the addition of antiestrogens," Carbone said. "Other studies are using adriamycin alone and in combination. In patients with high risk, what value is there in adjuvant therapy? We've seen that there are definite results, with simple therapy.

"How about those patients with negative nodes? If the treatment is simple and not dangerous, why not follow surgery with treatment for those with negative nodes?"

Carbone pointed out that if all patients with negative nodes were given follow up treatment, 75% of them would be treated unnecessarily. "But if we could find ways to identify those 25% who will recur, then we would have a group 100% of which should be treated."

Carbone is convinced that it will be possible to develop systems for identifying markers which show the presence of tumor cells, indicate the tumor level, and help determine the type of treatment, and the duration and intensity of treatment.

Most of the task force contractors already are collecting specimens and sera. "We're collecting these markers, now what are we going to do with them?" Carbone asked. He said the NCI statistical office has agreed to process the data, but the job of collecting and measuring the markers and compiling the data will have to be done elsewhere. He agreed that none of the contractors in the program would be asked to take on that task without additional funding. An RFP may be developed for that project.

"We've got to roll the ball down the hill," Ahmann said. "We've got a captive group, the investigators, the patients, and the data. Let's get on with it."

The question was raised several times during the meeting about the advisability of discontinuing the controls. Some doubt was expressed that there could be adequate evaluation without control groups. "Without controls, we don't have science," said committee member Olof Pearson, Case.

"I think we can match the large numbers we have, retrospectively and prospectively," Carbone said.

"Are you implying that we have adequate historical controls?" Pearson asked. "Yes," Carbone answered.

What should investigators do with patients in their studies who recur, Carbone asked the group.

Sparks said, "We tell patients that if the experimental treatment fails, we'll give them the best treatment available at that time."

"There's no definitive answer," Carbone said. "L-PAM failures have responded to the combination drugs. CMF failures have responded to adriamycin and vincyristine."

Christopher Longcope of the Worcester Foundation discussed the status of estrogen receptor studies being conducted at his institution. His group receives 50 tumors a month from Peter Bent Brigham Hospital, Univ. of Pittsburgh and Univ. of Southern California.

From October 1974 to August 1975, they received 432 tumors; 277 were assayed, and 156 were positive,

121 negative.

Eugene DeSombre, Univ. of Chicago, reported on the status of his estrogen receptor studies and proposed additional areas "for us or someone else to get into:"

1. Clinical correlations – include other parameters such as disease free interval, site of lesion, response to previous hormone therapies.
2. Mastectomy specimen for subsequent prediction of response to endocrine therapy.
3. Receptor antibody – RIA method for receptor content, methods to differentiate R plus and R minus.
4. Assay of other receptor proteins – prolactin, progesterone.
5. Receptor characteristics of breast cancer in oriental women – joint studies underway in Tokyo and Hong Kong.

Thomas Dao, Roswell Park, reported on the status of his estrogen receptor studies.

Dao previously had reported on his studies in which bilateral adrenalectomy with radical mastectomy had been performed on 17 postmenopausal women with breast cancer having metastasis in four or more nodes. Of these, 14 are living with no evidence of disease, six without recurrence five or more years since primary treatment. The study also demonstrated that adrenalectomy patients on hormone replacement therapy are able to lead full and active lives without complications.

The results show that both the recurrence and mortality rates are significantly lowered if a bilateral adrenalectomy is done after radical mastectomy as the initial form of treatment, Dao reported. "It is noteworthy that both the survival and the recurrence rates in historical controls are remarkably similar," he wrote. "The data perhaps would give credance to the conclusion the favorable outcome in patients with four plus positive nodes in this study is due primarily to the effect of the adjuvant adrenalectomy rather than other environmental or therapeutic factors. The study also demonstrated conclusively that adrenalectomy patients when adequately maintained on hormone replacement therapy are able to lead full and active lives for a long time. We have observed no complications or other problems in all these patients now living five or more years after adrenalectomy and radical mastectomy. . .

"The validity of the present data must await confirmation from extended clinical trials. How adrenalectomy exerts its effect to delay or destroy occult metastases supposedly existing in those high-risk breast cancer patients cannot be fully explained at the present time. Our laboratory is presently studying the effects of adrenalectomy on both hormonal and immunologic alterations in the host."

Of the three patients who had recurrence, one was age 69, with six of 24 nodes involved; one was 49, with six of 27 nodes involved, and one was 55, with seven of 25 nodes involved.

CYCLAMATE REVIEW COMMITTEE STARTS ITS SURVEY; FINAL REPORT DUE JAN. 15

Members of the Temporary Committee for the Review of Data on the Carcinogenicity of Cyclamate will fan out around the world starting this week to check out the 26 studies which have produced conflicting findings since 1969.

Certain members of the committee will make site visits to labs where tests were conducted, including those in Europe and Japan. They'll talk to investigators, inspect facilities, look at data and slides.

The cyclamate industry has criticized studies which found some evidence of carcinogenicity, results of which caused the Food & Drug Administration to remove the cyclamates from the so-called GRAS list (generally recognized as safe) several years ago. That action by FDA effectively banned the artificial sweetener from foods manufactured or distributed in the U.S.

But the carcinogenicity of cyclamates in animals has not been conclusively demonstrated. When and if that is done, the Delaney amendment would be invoked, which bans addition of any substance that causes cancer in animals from human food.

The review committee is charged with assessing the validity of tests already conducted, and may suggest what further studies might be needed, if any.

Arnold Brown, of Mayo and a former member of the National Cancer Advisory Board, is chairman of the committee.

The committee last week adopted a schedule which if followed will have its final report in NCI Director Frank Rauscher's hands by Jan. 15. The report of the foreign site visitors is due by the middle of October and the domestic site visitors by Nov. 1. The next meeting of the committee and working groups will be held before mid-November, when they will discuss in detail the studies they will have reviewed. The first draft of the report is due by mid-December.

Michael Sveda, the discoverer of cyclamates, appeared at last week's meeting to protest bitterly the makeup of the committee's membership, Brown's refusal to permit him to participate in the committee's deliberations and to ask questions of committee members, the motives of FDA, National Academy of Sciences, NCI and anyone who has questioned the safety of cyclamate.

Sveda read portions of a letter he sent to Rauscher in which he charged it was "impossible" for NCI to select an impartial committee on cyclamates "because the views of the committee members on cyclamates will be known to the selectors before the committee is selected. . . . The committee is captive because at least some of them, perhaps all of them, depend on you for their public dole of research funds to keep them alive professionally."

Sveda said, "Get out of the regulatory business, Dr. Rauscher. Your business is cancer research."

After Brown had told Sveda that he could have no more than 20 minutes to make his statement and could not take part in committee discussion, Sveda asked, "Is there anyone here who outranks this man?"

After no one spoke up, Brown said, "I guess not." Sveda fumed, threatening to take his case to Sen. Abraham Ribicoff (D-Conn.) and to the press.

HERE'S HOW CONSTRUCTION GRANTEES TO SPEND $30 MILLION IN FY 75 FUNDS

NCI officially announced this week fiscal 1975 construction grants previously reported in ***The Cancer Letter***. The 12 grants totaling $30 million were for both new construction and alteration of existing facilities.

The Ford Administration continues to oppose new construction funding by the federal government, although it did give in to pressure and threat of lawsuits to release the 1975 money. The White House appears headed for another confrontation with Congress and grantees over this policy.

Details on how the grantees will spend their money follow:

Albert Einstein College of Medicine of Yeshiva Univ., New York City, received $8,649,562 for construction of a multilevel building within the Einstein Medical Complex. The entire building will be utilized for cancer research and will cost approximately $12 million.

Under the leadership of Harry Eagle, a multidisciplinary cancer center program has been developed at Einstein that has made construction of the new building necessary. Major components of the program are studies involving carcinogenesis, anticancer drugs, tumor immunology and genetics, viral oncology, regulation of growth and function in normal and cancer cells, normal and malignant cell structure and metabolism. Clinical cancer research will be conducted on several floors of the building.

UCLA received an award of $5,062,500 to construct a portion of a 13-level building that will be the focal point of cancer research activities at the university. The facility will be built on the eastern side of the UCLA Medical School campus. Three levels below grade and a ground-floor level will be for cancer research. Upper floors of the new building will house the School of Nursing. Construction of the upper floors will be financed by state-appropriated funds totaling $4.4 million.

Biocontainment facilities for research involving viruses and cancer-causing chemicals will be on a lower level of the new building. Other levels will contain laboratories for research in medical and surgical oncology, immunology and cancer biology. A clinical area will be on the ground floor with examination rooms and offices for outpatient clinical studies.

Three years ago the university received an NCI grant of $3,139,537 toward the construction of a seven-floor cancer facility for its Molecular Biology Institute, established in 1965. This research institute contains many of UCLA's cancer-related basic science laboratories.

At New York Univ. Medical Center new construction and alterations for a basic and clinical cancer research facility are being funded in part by NCI for a total award of $3,353,765, with $704,072 supplied in FY 1975 and the remainder in FY 1976.

New construction will consist of a two-story expansion of the east wing of University Hospital to contain the avian and small mammal unit of the cancer center. In addition, this expansion will provide laboratory space to support clinical research for the oncogenetics and endocrine units.

Renovation and alteration are under way of specific areas in the Berg Institute in University Hospital and also in the Veterans Administration Hospital. In the institute major space components will be for work in cell biology, tumor immunology, membrane analysis and cell culture. Radiation therapy and nuclear medicine facilities at University Hospital will benefit from the alteration and renovation. Space for a clinical research unit of 20 beds will be provided at the VA Hospital.

In FY 1973 New York Univ. Medical Center received an NCI grant of $1,759,000 to construct an addition to the existing A.J. Lanza Research Laboratory at the Sterling Forest location of the Medical Center in Westchester County.

Cancer research facilities at Columbia Univ. will be expanded with the aid of a $5,890,095 construction grant to complete the interior of seven floors of existing shell space in the 17-floor Augustus Long Library-Health Sciences Center at the Columbia-Presbyterian Medical Center. Cost of construction of the Library-Health Sciences Center is estimated at $32.75 million.

In the new laboratories, cancer research will be conducted in cell differentiation and growth control, cytogenetics, nucleic acids and carcinogenesis, cancer viruses, and tumor immunology.

In 1973 NCI awarded a $530,271 construction grant to Columbia for alterations and fixed equipment on the fourth floor of the Presbyterian Hospital to develop a 21-bed clinical cancer research center unit. This grant also financed remodeling in the College of Physicians & Surgeons for an endocrine research laboratory.

At the Sidney Farber Cancer Center in Boston, the FY 1975 grant of $4,896,863 is for construction and fixed equipment to complete seven floors of existing shell space. Three years ago $6 million was awarded by NCI towards the cost of constructing the building, the Charles A. Dana Cancer Center. The research program housed in these facilities will include hematology, chemotherapy, pharmacology, clinical microbiology, immunology and immunotherapy.

The areas of uncompleted shell space in the 60%-completed building are part of the sub-basement, which will be used for radiation therapy, and the seventh through 14th floors. On three of the floors there will be an additional 96 beds for clinical research. Admission to the clinical facilities at Sidney Farber Cancer Center is restricted to patients involved in studies of cancer treatment. In addition, most patients are involved in disease-oriented laboratory research such as drug metabolism, tumor immunology, and cell kinetics.

Last March the Univ. of Chicago received a supplemental construction grant of $455,136 in additional funds to be used to meet NCI-imposed requirements for dealing with biohazards. In FY 1974, a grant of $4,291,352 was awarded to the university for new construction and some remodeling to provide space for research in virology, cell biology, radiotherapy, radiation physics, and for clinical research.

The award of $1,274,372 to Yale Univ. School of Medicine is to complete the construction grant funded substantially but not completely in FY 1974. In that year Yale received $3,648,359.

A new connecting brdige will link at the second-story level the Winchester Building (inpatients) with the Institute of Human Relations Building (research), and will contain administration offices of the comprehensive cancer center, a library, and some laboratory facilities. Other renovated or newly constructed laboratories will house research in developmental therapeutics and virology, and studies involving electron microscopy and radioisotopes. Space for additional beds for clinical investigation is also being constructed.

In FY 1972, Yale received $1,279,217 to aid in the building of a four-story clinical cancer research facility with clinical pharmacology and chemotherapy laboratories to expand existing laboratory space.

Memorial Sloan-Kettering Cancer Center, New York City, was awarded $199,612 for three construction projects to develop biohazard containment and control capabilities. An independent air-circulation system and laminar flow hoods will be installed in the viral research laboratory in the Kettering Laboratory Building to remove potential hazards. A small area of the 11th floor of the Ewing Hospital will be converted into a biological containment unit for short-term projects involving viruses. Installation of a radiation-safe working area in the cyclotron facility in the basement of the Kettering Laboratory will include two "hot cells" to handle the icnreasing amounts of radioactive material produced in the cyclotron facility. Production of labeled biochemical substances using short-lived positron (positive electron) emitters for tumor localization studies has expanded substantially. The new equipment will remove a serious limitation on the chemical processing time available to produce usable amounts of radiopharmaceuticals.

An award of $4,862,494 was made to the Memorial Sloan-Kettering Cancer Center in FY 1974 to remodel portions of the James Ewing Pavilion, a 12-story building adjacent to both the Howard Laboratory Building of the Sloan-Kettering Institute and the old and new portions of Memorial Hospital. The remodeling provides research space for the human cancer program, one of the eight major research programs of this comprehensive cancer center.

In FY 1973, the center received $1,570,000 in NCI construction grants for renovations in the old Memorial Hospital building and to develop an emergency electrical generating system for the Kettering Laboratory.

The Salk Institute for Biological Studies, La Jolla, received a construction grant of $1,800,000 for a two-level underground facility for experimental animals.

For basic cancer research facilities, Washington Univ. School of Medicine, St. Louis, was awarded $733,438 to complete shell space on the eighth floor of the McDonnell Sciences Building. Fixed equipment totaling $250,000 is included in the overall construction grant. Electron microscopy will be used to investigate the nucleic acid of animal viruses. The new facilities will be utilized principally for the production and purification of large batches of virus and of large quantities of cells from well-established cell lines.

The Michigan Cancer Foundation in Detroit received $184,350 for remodeling of facilities for its expanding breast cancer research program. A low-temperature storage area will be provided in the basement. Laboratories for work in cell physiology and immunology and space for staff support will be created on the second floor.

In its breast cancer program, the Michigan Cancer Foundation correlates a large quantity of clinical materials with fundamental research laboratory data. Approximately 200 breast cancer specimens are studied each year using biological, biochemical and immunological parameters. After these initial studies, the tumor specimens or their cultured cells are kept in the low-temperature storage bank for possible future investigation. The low-temperature bank will also store patients' blood sera for comparative studies before and after treatment, during remission, and at the time of recurrence.

The foundation was awarded $200,000 three years ago for a human virus containment laboratory in its new cancer research building.

A grant of $150,000 was awarded to the Tufts Cancer Research Center, Boston, to renovate part of the third floor of the South Cove Building for a laboratory suite with essential mechanical room space, including a coldroom, warmroom, tissue culture room, and also an office. The newly available space will be used for research in the mechanisms of hormone action on target cells grown in culture.

RFPs AVAILABLE

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

RFP NCI-CP-VO-61008-63

Title: *Transcriptional regulation of eukaryotic gene sequences*

Deadline: *Nov. 1*

The Virus Cancer Program will make available to interested contractors a request for proposal to study transcriptional regulation of eukaryotic gene sequences. A possibility to explain the stochastic appearance of human breast cancer is to postulate the loss of genetic control of the portions of breast cell DNA responsible for cancer induction.

Some lines of evidence suggest that there is no horizontal transmission in human cancer (infectivity); mouse mammary tumor virus can be genetically transmitted; and the most common site of genetic regulation in the cell is at the level of DNA to RNA transcription. Therefore, an understanding of the regulation of transcription is central to an investigation designed to characterize and control the breast cancer induction process.

The objective of these studies is to develop an approach to inherited viral gene control utilizing specific biochemical, biologic and/or immunologic information. Recent advances using specific viral probes for viral gene sequences in mammalian DNA have opened the possibility of both an understanding of mammalian transcription, and an insight into regulation of potentially oncogenic viruses in differentiated tissues like the mammary gland.

Contract Specialist: Jacque Labovitz
Cause & Prevention
301-496-6496

RFP NCI-CB-64013-39

Title: *Development of an immunodiagnostic method for the early detection of overian cancer in asymptomatic women*

Deadline: *Oct. 30*

Develop an immunodiagnostic method of identifying the existence of ovarian cancer at an early stage of the disease and for serial monitoring of patients with ovarian cancer so that treatment can be more effective.

Contract Specialist: Thompkins Weaver Jr.
Biology & Diagnosis
301-496-5565

RFP NCI-CB-64011-35

Title: *Development of specific immunoglobulins labelled with gamma-emitting radioisotopes for external detection of tumors*

Deadline: *Oct. 30*

Develop a procedure for tumor detection, making use of purified immunoglobulins, with specific antibody reactivity to tumor associated antigens, which are suitably labelled with gamma-emitting radioisotopes so that tumors can be detected and located within the body by external scanning. Success of the procedure will depend upon the selective binding of the gamma-labelled tumor specific immunoglobulins by the target tumor tissue.

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

SOLE SOURCE NEGOTIATIONS

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

Title: Tissue interactions in induction and perpetuation of hormonally-induced permanent cellular alterations

Contractor: Stanford Univ.

Title: Relationship of pituitary hormones and andorgens on prostate metabolism

Contractor: West Virginia Univ.

Title: Synergistic interaction of hormones and neutron radiation mammary gland carcinogenesis

Contractor: Brookhaven National Laboratory, Upton, N.Y.

CONTRACT AWARDS

Title: Research into computer accessed bibliographic and citation data

Contractor: Institute for Scientific Information, Philadelphia, $28,284.

Title: Operation and maintenance of the DR&D biological data system

Contractor: Value Engineering Co., Alexandria, Va., $693,460.

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