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"SLOPPY" CANCER CONTROL GRANT APPLICATIONS TURNED DOWN AT TWICE NIH DISAPPROVAL RATE

NCI's Cancer Control Grant Review Committee has been disapproving from two-thirds to three-fourths of the grant applications it has received, nearly twice the disapproval rate of most other NIH grant review study sections.

Executives of the Div. of Cancer Control & Rehabilitation blame the high disapproval rate on various factors. "Mostly, they're just sloppily prepared, poorly written applications," one DCC&R staff member told *The Cancer Letter.*

Many of the applications have been coming from organizations which have little or no experience in grant writing. The nature of the division's grants program is such that smaller institutions, many with no academic

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In Brief

BYRD HEADS ACS, LEE CLARK PRESIDENT-ELECT; NCI NEEDS COMMUNITY MEDICAL ONCOLOGIST

BENJAMIN BYRD, Tennessee surgeon and chairman of the American Cancer Society task force on breast cancer control, is the new ACS president. Byrd is clinical professor of surgery at Vanderbilt and Meharry Medical College. R. Lee Clark, member of the President's Cancer Panel and president of the Univ. of Texas System Cancer Center, is ACS president-elect. . . . **MEDICAL ONCOLOGIST** "sensitive to community programs and problems" is needed by NCI's Div. of Cancer Control & Rehabilitation. The position, on the staff of Laurence Callan, associate director for community activities, is GS-15 grade, pays $36,000. Contact Callan, 301-427-8204. . . . **FORMAT CHANGE** for the November National Cancer Advisory Board meeting. This time it's only two days instead of three, Nov. 17-18. All but first 15 minutes of the first day is closed for grant review. Tuesday morning, Nov. 18, the Board will hear reports from Philippe Shubik, chairman of the Subcommittee on Environmental Carcinogenesis, and Alan Rabson, director of the Div. of Cancer Biology & Diagnosis, on recommendations and options proposed regarding programs and activities on interferon therapy. More grant reviews are scheduled for closed session Tuesday afternoon. . . . **IF VINYL CHLORIDE** were just coming into use today, would present detection, screening and regulatory systems recognize its carcinogenic potential in time to prevent the widespread use that has occurred over the last 10-15 years? "I'm inclined to say they would," responded James Peters, director of NCI's Div. of Cancer Cause & Prevention, to Benno Schmidt's question. But Norton Nelson of NYU Medical Center said that was "over-optimistic. A paper was published in 1970 that showed vinyl chloride was capable of producing cancer, yet nothing was done. That tells us that it takes a message of strength we haven't yet achieved to get it across to the public and government officials."

NCI OFFERS GUIDELINES TO HELP CANCER CONTROL GRANT APPLICANTS

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affiliation, are encouraged to seek control and rehabilitation grants.

"They need help in writing their applications," the NCI executive said. "They should seek out the assistance of someone, or some other institution, with experience in writing grants. That alone would substantially improve the quality and cut down on disapprovals."

The rejected applications aren't all coming from the unsophisticated, however. "Some of these guys who have lost funding for their existing programs are looking desperately for some way to keep them alive. They try to bend them to make them fit, or appear to fit, our needs," the executive said. "That won't work with us. Our people are sharp enough to spot that kind of thing."

The major deficiency, in addition to the sloppy writing, is the failure of many applicants to address themselves to the needs of the cancer control program. To help resolve that problem, NCI has put together a set of guidelines for the DCC&R grants program. Careful attention to those guidelines by applicants would dramatically improve their chances for funding. The guidelines follow:

"Under the National Cancer Plan, the Div. of Cancer Control & Rehabilitation has the principal federal responsibility for assuring the rapid and effective application of cancer research findings in the prevention, detection, diagnosis, and treatment of cancer and the rehabilitation and continuing care of cancer patients. It is the ultimate DCC&R goal to reduce the incidence, morbidity, and mortality from cancer through a five-pronged effort:

"1. Identification of new methods, knowledge, and techniques that may be applicable to control activities.

"2. Field testing of potential control knowledge and techniques in limited community field trials to determine their potential for widespread community usage.

"3. Evaluation of potentially useful control knowledge and techniques to determine their effectiveness, practicality, acceptability, impact on the disease, and economic or cost-benefits prior to embarking on costly widescale community demonstration and promoting efforts.

"4. Demonstration of effective, practical, control knowledge and techniques to assure their rapid widespread utilization in all areas in the nation.

"DCC&R is concerned with the entire scope of the cancer problem, from the prevention of the disease to the rehabilitation and continuing care of the cancer patient during and after treatment. Program thrusts, therefore, are in three major intervention areas: (1) prevention; (2) detection, diagnosis and pretreatment evaluation; and (3) treatment, rehabilitation and continuing care. DCC&R activities are supported by either grants or contracts. The most appropriate support mechanism will be determined on an individual project basis. The following actiyities relate to grants only.

"The grant-support portion of this national program encompasses all three intervention areas. It is intended: (1) to allow the initiation of new concepts in a more effective utilization of existing procedures and/or techniques, and (2) to provide information on the refinement of established procedures and/or techniques for a more vigorous prosecution of cancer control. The DCC&R is not involved in (1) performing regulatory functions, or (2) the support of delivery of health care, per se. DCC&R does not support the usual laboratory and clinical research to develop new techniques and procedures. Since this grant program is not intended to duplicate the contract programs in the DCC&R, applications duplicating current RFPs or existing contract programs will be returned. It is in this context, therefore, that grant applications directed to the subject matter indicated above will be received and accepted. Because exceptions may exist, it is advisable to consult with the DCC&R staff to determine if a proposed study will fit within the above guidelines.

"Grants may be utilized as a mechanism for support in the following areas:

"PREVENTION

"1. The application of identified methods and techniques to inform and stimulate health professionals and the public to fully utilize available cancer prevention services. Such projects are to be oriented toward avoiding the occurrence of the disease through prevention efforts, especially methods and techniques for reducing the exposure to carcinogens, and must include the testing and evaluation of all preventive activities proposed.

"2. Programs for the development of cessation strategies involved with cigarette smoking and alcohol consumption.

"3. Programs for understanding the determinants of consummatory behavior as they relate to cancer prevention strategy.

"DETECTION, DIAGNOSIS, AND PRETREATMENT EVALUATION

"1. The assessment and evaluation of screening/detection systems with special emphasis on determining the appropriate interval of screening procedures and the cost-effectiveness of various screening-detection systems.

"2. Studies designed to develop a better understanding of the factors which motivate and/or inhibit primary health care personnel and the public from dealing more appropriately with early detection, diagnosis, and pretreatment evaluation.

"3. Innovative studies designed to improve the techniques and procedures for effective utilization in

appropriate settings of professional assistants in the detection/diagnosis of cancer.

"4. Studies to re-evaluate presently accepted or evaluate newer methods for pretreatment evaluation and to promote the development of criteria and standards for pretreatment evaluation directed toward defining adequate, acceptable, and structured approaches to pretreatment evaluation of the patient as required to choose the most appropriate treatment regimen.

"REHABILITATION/CONTINUING CARE

"1. Research on the management of pain in cancer patients.

"2. Research studies on the psychological and psychosocial aspects of cancer as it affects the patient, the patient's family and health professionals. This area may include:

"a. The development of new procedures and techniques for counseling cancer patients, their families, and the health personnel dealing with cancer patients.

"b. Studies of attitudes and behavior as they relate to the delivery of rehabilitation and continuing care.

"3. Research studies on the dietary and nutritional management of cancer patients (especially those patients undergoing aggressive or palliative therapy) including feeding behavior, their alteration by disease and/or treatment and restoration toward normal feeding.

"4. Studies for new approaches to the rehabilitation problems of head and neck cancer patients in relation to cosmesis, speech, and swallowing. These approaches may involve new materials and procedures, as well as new uses of existing approaches and procedures.

"5. Studies for the development of new physical techniques/procedures to rehabilitate cancer patients with specific deficits (paraplegia, stoma, etc.) to the extent that these techniques are of primary benefit to cancer patients.

"6. Studies for the development of new concepts and procedures for the continuing care of cancer patients with the disease in varying states of control.

"7. Studies of social factors in relation to the patterns of rehabilitation and continuing care to include level of care received, impact of care and of alternative approaches for the patient, family, and community, including health professionals.

"SPECIAL COMMUNITY RESOURCE DEVELOPMENT

"Under this general area of cancer control, applications are to be concerned with the development of community outreach programs through NCI's designated comprehensive cancer centers and multiprotocol clinical cooperative groups.

"APPLICATION REQUIREMENTS

"Applications should be submitted on PHS grant application form NIH 398 which should be mailed to: Div. of Research Grants, NIH, Bethesda, Md. 20014.

"Applicants should type CANCER CONTROL in the top margin of the application's face page. A covering letter should also identify the application as a response to the cancer control program. A copy of this letter and any inquiries should be directed to Dorothy Brodie, program director for grants, Div. of Cancer Control & Rehabilitation, NCI, Blair Bldg Room 628, NIH, Bethesda, Md. 20014. Telephone: 301-427-7990.

"An application submitted in response to this announcement and so identified provides assurance only that the application will be considered for assignment to this program area and not a commitment for such assignment. DRG in collaboration with funding unit staff will make assignments to funding units whose program best fits the substantive contents of the application as presented."

Applicants are encouraged to contact DCC&R staff members before submitting their proposals. "We'll be glad to talk with them," the NCI executive said. "There is no reason why they should waste their time and ours with proposals that have no chance of being funded."

The division is funding $5.8 million in fiscal 1976. Here are some examples of individual grants with estimated 1976 funding:

Pain control through hypnosis in childhood cancer, Stanford Univ., $30,000.

Mathematical model for screening cervical cancer, Boston Univ., $41,000.

Psychological adaptations to childhood leukemia, St. Jude's Children's Hospital, $69,000.

Cancer answers and rights information system, Univ. of Virginia (Richmond), $43,000.

Cancer control and prevention program, American Health Foundation, $674,000.

Teaching techniques for breast cancer detection, Cancer Research Center, Columbia, Mo., $44,000.

Psychosocial aspects of cancer rehabilitation, West Coast Cancer Foundation, $210,000.

Electronic laryngeal prosthesis, Univ. of Texas (Galveston), $80,000.

Clinical and research radiation therapy in cancer care, Thomas Jefferson Medical College, $916,000.

Cancer control developmental grant, Univ. of Alabama, $554,000.

Cancer control outreach program, Roswell Park, $258,000.

NCI PROPOSES TO DETERMINE EFFICACY OF BIENNIAL BREAST CANCER SCREENING

Evidence coming in from the NCI-American Cancer Society breast cancer screening demonstration projects indicates that annual screening by mammography substantially reduces breast cancer deaths among those so screened.

The expectation of reduced death rates is based on

earlier detection of breast malignancies, before they spread into the axillary nodes. About 80% of the cancers being found in the screening projects are stage I.

The program so far has supported the findings of the New York HIP (Health Insurance Plan) study in the 1960s which found that annual screening led to a one-third reduction in the breast cancer death rate among 31,000 women in the study.

The value of annual screening is no longer in doubt, although questions have been raised by NCI's John Bailar and others (***The Cancer Letter,*** Oct. 17) about the hazards of radiation exposure. NCI is now asking the question, would biennial screening be as effective as annual checkups?

William Pomerance, chief of the Diagnosis Branch in NCI's Div. of Cancer Biology & Diagnosis, outlined to the Cancer Control & Rehabilitation Advisory Committee last week a proposal to add another year to the NCI-ACS program and find out if screening loses any of its effectiveness done every other year instead of every year.

The public health implications could be significant. Screening costs could be cut in half, if biennial checkups are developed as the norm. Or, as Robert Connors of NCI's Biometry Branch said, for the same money and medical manpower, twice the number of women could be screened.

Also, obviously, women being screened once every two years would receive half the radiation exposure of those those receiving mammograms every year.

Connors said that two to three breast cancer deaths per 1,000 are expected among those screened annually. The rate per 1,000 for those not screened is four, with the average of annual screen and no screen 3.25. "If we find that the rate for women in a biennial screening program is less than 3.25, then (considering costs and other factors) it would be better than the annual program," Connors said.

The 27 centers participating in the NCI-ACS project are committed to conducting the annual screens for six years. The new proposal would extend that to seven years, and the followup would extend for five years after the last group is screened. The final answers would not be available until 1989.

"We have no real basis for screening every year," Pomerance said. "There's no rationale except that it is convenient to say one year."

Pomerance assured the committee that no woman would be denied the annual screen against her wishes, and that the program and all the various risks would be fully expalined to all participants.

Arthur Holleb, member of the committee and ACS vice president for medical affairs and research, said he would go along with the proposal. "I would love to have the answer. There are 45 million women at risk, and we can't screen them all."

The committee generally approved the proposal and recommended that NCI staff proceed.

ABSTRACTS OF PAPERS FROM MEETING OF THERAPEUTIC RADIOLOGISTS

The 17th annual meeting of the American Society of Therapeutic Radiologists was held in San Francisco last month. Selected abstracts of papers presented at the meeting appear below, and others will be published next week. Copies of complete papers are available. Write to ***The Cancer Letter*** *and include title and authors of papers desired.*

Effects of Radiation on Immunocompetence – ***J.R. McLaren & Z.L. Olkowski, Emory Univ.***

Most of the radiobiological variable including anatomical location of the tumor, kinetics of tumor cells, proportion of hypoxic cells and the radiosensitivity of the tumor are independent of the host. The outcome of radiation therapy depends not only on these variables but also on the immunity of the tumor-bearing host.

Probably the most important factor in the curability of cancer within patients is their immunocompetence. The potential of the host to eradicate tumor cells depends on two fundamental types of immune responses; cellular immunity (T-lymphocytes) and humoral immunity (B-lymphocytes).

To study the effects of therapeutic doses of ionizing radiation on cellular immunocompetence of patients undergoing radiation therapy for carcinoma of the breast, squamous cell carcinoma of the cervix and head and neck the level of circulating T-lymphocytes was monitored before, during and after the treatment.

Lymphocyte cytotoxicity and serum toxicity was also evaluated in patients with squamous cell carcinoma before the treatment and following the end of radiation therapy.

The control group consisted of 51 healthy volunteers. Control individuals had a mean 75% of T-lymphocytes and 1460 T-cells per 1 cmm. Their lymphocytes were cytoxic to SCC target cells and their heat inactivated serum enhanced this toxic activity

Most of our patients tested before radiation were characterized by decreased percentage as well as decreased absolute numbers of circulating T-lymphocytes. In advanced metastatic cases of SCC, lymphocytes isolated from the peripheral blood of these patients were only slightly cytotoxic to SCC target cells. Addition of heat inactivated patient's serum to the mixture of patient's lymphocytes and SCC target cells resulted in the lack of cytotoxic activity indicating the presence of blocking activity of serum.

Following radiation therapy the percentage and absolute numbers of T-lymphocytes in tested patients increased in comparison to pre-treatment values. Four to six weeks after the end of radiation therapy lymphocytes from some of our patients who clinically responded well to the treatments showed increased cytotoxicity to the target tumor cells and their serum did not block this toxic activity.

Oat Cell Carcinoma of Lung: Reappraisal of Current Management – ***Chan Choi, Robert Carey, Herman Suit, Chiu-Chen Wang, & Milford Schulz, Massachusetts General Hospital***

Relative roles of radiotherapy, chemotherapy and planned combination radiotherapy and chemotherapy were reviewed by analyzing 190 patients registered at the Massachusetts General Hospital Tumor Registry between 1968 and 1974. Median survials are 9 months and 4 months for those with localized and extrathoracic extension respectively.

If we consider the group of patients treated between 1968 and 1971 as a historical control because of radiotherapy being the main form of treatment and multiple drug combination chemotherapy being introduced in 1972, then relative roles of multiple drug combination chemotherapy could be assessed by comparing results obtained between 1972 and 1974 (Study Group) to that of the historical control group. For those with extrathoracic extension, yields of long term survivors (–9 months) were 1.5% (1/63) and 7% (6/78 for historical control and Study Group respectively. However, for those with localized lesion, no increase of long term survivors was noted by addition of multiple drug aggressive chemotherapy to radiotherapy in the recent study group; yields of long term survivors were 60% (14/23) and 46% (12/26) for the historical control and Study Group respectively. Thirty-three patients survived nine months or longer and all except two were treated with primary radiotherapy or a planned combination radiotherapy and chemotherapy.

The Role for Radiotherapy in the Treatment of Chronic Lymphocytic Leukemia – ***Ralph Johnson, NCI***

Total body irradiation with small fractionated doses has produced complete clinical and hematologic remission in one-third of patients with active, symptomatic disease. These remittors have experienced quantitative and qualitative changes in the status of their illness which were not observed in patients with less complete response or patients treated only with chemotherapy, namely a return to normal performance, recovery from pretreatment hypoimmunoglobulinemia, absence of serious infectious complications, and marked prolongation of survival. This constitutes the first evidence that the natural history of chronic lymphocytic leukemia can be materially altered by treatment.

Adjuvant Methotrexate in the Radiotherapeutic Treatment of Advanced Head and Neck Tumors – ***Robert Lustig, Paul DeMare, & Simon Kramer, Thomas Jefferson Univ. Hospital***

From 1961 to 1965, 57 patients with advanced head and neck tumors were treated with oral methotrexate and radiation therapy. The three-year survival was previously reported as 18 of 57. From 1968 to 1972, 84 patients were entered in a randomized study of radiation therapy with and without I.V. methotrexate. Minimum three year survival in this group is 8 of 33 patients in those receiving methotrexate and 1 of 33 in those receiving radiation alone.

Management of Post-Operative Recurrences of Malignant Salivary Gland Tumors – ***Robert Kagan, Herman Nussbaum, Steven Handler, Robert Shapiro, Harvey Gilbert, Melville Jacobs, John Miles, Paul Chan & Thomas Calcaterra, Southern California Permanente Medical Group, UCLA Medical Center, City of Hope***

The clinical source of 130 patients treated for malignant paratoid tumors at the three contributing institutions have been retrospectively reviewed in detail. Fifty-six of these patients developed recurrence following their primary treatment by surgery alone. Clinicopathologic review revealed several criteria of malignancy which predispose to recurrence. There were a total of 109 recurrences among these 56 patients. The average number of recurrences was 2 per patient and the median time to first recurrence was 3.7 years.

Once recurrence developed, treatment was by surgery, irradiation, chemotherapy or a combination of these. Median survival from time of recurrence was 2 years with a range from 0.5 to 17 years. Of these 56 patients, 33 are dead, 9 are alive with disease and 14 (most less than 5 years) are alive with no evidence of disease. The patients who are NED have had an average of 1.6 recurrences and a median survival of 3 years. Treatment of the recurrences by any method appears inadequate (more than 75% of the time) and success is not related to radiation dose. The authors conclude that when future malignant salivary tumors are initially excised, a trial of wide field post-operative radiation with a field of 6000 rads be administered.

Complications of Irradiation Related to Apparent Drug Potentiation by Adriamycin – ***Eric Mayer, Silvio Aristizabal, Max Boone, Robert Miller & Robert Heusinkyeld, Arizona Medical Center***

A new antitumor agent, hydroxydaunorubicin (adriamycin) is being used against an increasingly wide spectrum of malignancies. In this context many more patients are being treated with combinations of irradiation and adriamycin, either as a planned attempt at combining modalities or in an unplanned fashion, sequencing the two in a variety of ways and in different doses.

Fourteen patients have now been observed to have developed severe and prolonged normal tissue reactions during or after a course of irradiation. In all cases, they had also been treated with antitumor agents, the one common agent in every patient being adriamycin. Reactions have involved skin, lung, heart, and esophagus and have been unusual in terms of severity, duration and temporal relation to irradiation.

It would appear that a standard dose of adriamycin would be equivalent to a dose of irradiation on the order of 1000 rad.

More attention must be given to possible deleterious effects relating to the use of adriamycin in combination with ionizing radiation, and appropriate dose schedules will need to be established.

Radiotherapy in the Management of Primary Gliomas Involving the Intracranial Optic Nerves and Chiasm: A Review of 9 Cases Treated with Megavoltage Irradiation – ***David Harter, Jesus Caderao & Milam Leavens, M.D. Anderson***

In a review of more than 400 cases of primary neoplasms of the central nervous system treated at M.D. Anderson Hospital between 1944 and 1974, nine primary gliomas of the intracranial optic nerve and chiasm were found. Despite its rare occurrence, more than 500 cases of these gliomas have been described in the literature in the past 150 years. However, the role of megavoltage radiotherapy in the management of these tumors–which if uncontrolled, cause progressive visual loss, blindness and eventual deaht–is not described in the English literature. Eight of the nine M.D. Anderson patients completed a course of megavoltage irradiation. All nine patients had undergone transfrontal craniotomy and suprasellar dissection but none had had resection of the primary tumor. Doses ranged from 5000 rads in 5 weeks to 6000 rads in 7 weeks. Five patients are alive and free of disease at 1, 2½, 4, 7, and 7½ years. Six of 8 patients had improved vision following treatment. No macular or retinal degeneration or central artery thrombosis was encountered. And, although none has clinically apparent endocrine abnormality attributable to the treatment, an extensive pituitary evaluation is currently being performed on all survivors.

Radiation Therapy and C Parvum in the Treatment of Murine Tumors – ***Herman Suit, Robert Sedacek, Miles Wagner, Leo Orsi, Ronald Cisneros & Steven Echetler, Massachusetts General Hospital***

Corynebacterium parvum has been investigated as an immunopotentiator or augmentor of host reaction against tumor in three murine tumor systems: a fibrosarcoma, a squamous carcinoma and a mammary carcinoma. These tumors have been studied as early generation isotransplant. Experiments have been completed which assess the efficacy of C parvum when administered intravenously, intralesionally or subcutaneously, either singly or multi-route injections and achieving retardation of growth and permanent regression of established tumors of these three lines.

Of special interest has been the data from the complete radiation dose tumor control response assays in normal mice and in mice pre-treated with C parvum. C parvum was given intravenously and intralesionally or both intralesionally and intravenously prior to or following irradiation; radiation administered in single or multi-doses. For example, the data for the fibrosarcoma show a very marked reduction in radiation dose required to achieve destruction of tumor on the average. The efficacy of the C parvum was less for the squamous carcinoma and barely perceptable for the mammary carcinoma.

Can Pelvic Irradiation Be Omitted in Patients with Pathological Stage IA and IIA Hodgkin's Disease? – ***Robert Goodman, Anthony Piro, & Samuel Hellman, Harvard Medical School***

The treatment of early stage Hodgkin's disease has evolved from involved field irradiation to extended fields and in some centers to total nodal irradiation. Recently, involved field irradiation with chemotherapy has been investigated by others. It is the purpose of this report to demonstrate the efficacy of mantle and para-aortic irradiation in pathologically staged supradiaphragmatic IA and IIA disease.

From April, 1969, to December, 1973, 81 unselected laparotomy staged IA and IIA patients were treated at our center. Mantle and para-aortic (including splenic pedicle) fields were treated with a 4 or 8 MeV linear accelerator to 3600-4000 rad in 3½ to 4 weeks. Histologic types included 17 lymphocyte predominance, 35 nodular sclerosis, and 25 mixed cellularity. Median follow-up was 31 months (range 12-68). There was one relapse in 25 stage IA patients, and 5 in 56 stage IIA. Relapses were not related to histologic type. They included three true recurrences, two extensions, and one extra nodal (bone) dissemination. There were no pelvic recurrences. One patient died of radiation pneumonitis at three months, and one died of intercurrent disease at 22 months; neither had evidence of active disease. In srage IA patients, relapse free survival is 95% with no deaths, stage IIA patients a relapse free survival of 86%, and a 93% actual survival; only one patient died of disease.

These results strongly suggest that pelvic irradiation is not necessary in pathologically staged supradiaphragmatic IA and IIA Hodgkin's disease. Further reduction in radiation volume with the addition of chemotherapy is being performed in some centers. With the results reported here, the risk-benefit ratio of combined chemotherapy-radiation programs must be analyzed critically before adding chemotherapy to a more limited radiation regime.

Bone Marrow Regeneration After Combined Chemotherapy and Radiation Therapy – ***Philip Rubin & Charles Scarantino, Univ. of Rochester School of Medicine & Dentistry***

The bone marrow organ is the limiting tissue for combined radiation and chemotherapy studies. During the past three years, we have explored in depth the quantitative mechanisms of bone marrow regeneration in New Zealand white rabbits utilizing clinical fractional dose schedules of radiation on the hind and fore limbs of these animals.

Combination patterns of cytoxan and radiation therapy are being studied to determine the best sequence which will afford rapid regeneration of bone marrow. Preliminary evidence suggests that chemotherapy prior to irradiation allows for more rapid regeneration than does the reverse sequence of these therapeutic modes.

The Potential Cure of Advanced Hodgkin's Disease with Combination Chemotherapy and Irradiation – ***Leonard Prosnitz, Leonard Farber, James Fischer & Joseph Bertino, Yale Univ.***

A new program for the treatment of advanced Hodgkin's disease with combination chemotherapy and low dose radiation to the sites of bulk disease (nodal or parenchymal) was described by us previously and the preliminary results published (Radiology 107:187, 1973). Sixty-eight patients have now been treated with this program. Forty-nine (72%) have achieved a complete remission. More significantly, only 5 of 49 (10%) have relapsed with follow-up from 1-6 years. The cumulative survival at 5 years of patients entering complete remission is 90%. For patients not sustaining a complete remission it is 11% at 3 years. The cumulative survival of the entire group (responders and nonresponders) is 65% at 5 years. No patient has relapsed after 18 months. This program has achieved substantially greater disease free survival than has previously been reported. A significant number of these patients may well be cured of their disease.

Management of Malignant Pleural Mesothelioma by Surgery and Radical Radiotherapy Combining Photons and High-energy Electrons – ***Anthony Fuller, Gerald Randall, John Kyu Loh, Madhu John & Nael Martini, Memorial Sloan-Kettering***

The prognosis of patients with malignant pleural mesothelioma is consistently grave regardless of the treatment or combination of treatments given. Radiotherapy must be designed to include as much of the parietal and visceral pleural surfaces as possible without exceeding pulmonary tolerance. There are several technical problems associated with such a treatment scheme. Overdosage will lead to irreversible, disabling pulmonary damage, while underdosage will result in treatment failure.

A regimen has been devised for radical post-operative irradiation. Full hemithoracic bath treatments are given initially. Opposing anterior and posterior ports with lung blocks are employed and 5,400 rads in 8 weeks, as a split course, is delivered. The areas shielded by the lung blocks are treated with betatron-generated electrons of appropriate energy. The spinal cord is blocked posteriorly at an appropriate dose level. One of two patients so treated is surviving 40 months following completion of therapy, is fully functional and without evidence of either radiation-induced pulmonary damage or active disease.

Radiotherapy for Hemangiopericytoma: Report of New Cases and Review of the Literature – ***Joaquin Mira & Joseph Fortner, Methodist Hospital, Houston***

The response to radiotherapy of 11 patients with hemangiopericytoma treated at Memorial Hospital was analyzed and results compared with those reported by others. Twenty-nine courses were given to the 11 patients. Several degrees of response were noted in 26 instances with complete gross regression in 14 courses. Most of these were given doses above 3,000 rads. Tumors which responded poorly or not at all, received doses below 2,500 rads or were very large tumors.

Slow response is the rule. The average local disease free interval was 26.7 months. Recurrences occurred in 6 instances, unrelated to dose or degree of response. Late recurrences are not uncommon.

These results indicate that hemangiopericytomas, although they regress slowly, are responsive to irradiation, and belie allegations of radioresistance found in the literature. Radiotherapy produces a sizable local disease free interval. Late recurrences demand long follow-up. Strategy incorporating local excision of gross tumor, and wide field high dose radiation therapy for local control, are worthy of trial, and promise to reduce the relatively high incidence of recurrence after surgical excision.

Abdominal Irradiation of Non-Hodgkin's Lymphomas – ***D.R. Goffinet, Z. Fuks, E. Gla tstein & H.S. Kaplan, Stanford Univ.***

Eighty-nine mesenteric lymph node biopsies were performed in the first 132 previously untreated patients who underwent staging laparotomies at the Stanford Univ. Medical Center and 46 of these (52%) were involved by lymphoma. Since the standard inverted Y method of subdiaphragmatic irradiation fails to include the entire mesenteric area, whole abdominal radiation techniques have been recommended for patients with non-Hodgkin's lymphomas.

The records of 100 patients whose lymphomas were classified according to the scheme of Rappaport and who received inverted Y or para-aortic irradiation were reviewed. Subdiaphragmatic extensions and less frequently recurrences took place in over 50% of the patients with diffuse histiocytic lymphomas (22 of 42) and in 19% of those with nodular, poorly differentiated lymphocytic lymphomas (6 of 32). A new technique of whole abdominal irradiation, consisting of 1500 rads to the whole abdomen with anterior-posterior ports and full thickness lead blocks over the right hepatic lobe, followed by horizontal decubitus equal lateral fields to 3000 rads and finally an addi tional 1400 rad boost with wide para-aortic A.P. ports has been used at Stanford since 1973. This technique of whole abdominal radiation used in over 50 patients to date has led to a decreased incidence of radiation hepatitis, radiation enteritis and apparently fewer subdiaphragmatic relapses when compared to our prior abdominal radiation techniques.

Lymphangiography in Prostatic Cancer: Histopathologic Correlation – ***Ronald Castellino, Gordon Ray, John Salzman, David Pistenma, Edwin Meares & Malcolm Bagshaw, Stanford Univ.***

The value of lymphangiography in the staging of patients with prostatic carcinoma has remained unclear because of the lack of relevant clinical studies. Previous reports have dealt with highly selected groups of patients, and therefore, have been of limited value. This report deals with 44 consecutive, randomly chosen patients who underwent transperitoneal laparotomy and selective node biopsy within two weeks of bipedal lymphangiography.

Four of 21 patients (19%) with stage B disease, and 12 of 23 patients (52%) with stage C disease had positive lymph node biopsies. All patients had negative bone scans and bone marrow biopsies. There was agreement between lymphangiographic interpretation and the results of subsequent lymph node biopsies in 30 of 44 patients (68%). Ten of the 14 incorrect interpretations were due to positive biopsy results in patients with normal lymphangiograms; a false-negative rate of 22%. Four of these 10 patients had only microscopic foci of tumor not distorting the architecture of the node. The false-positive rate was 9%.

Special Set-up Techniques for Radiotherapy of Malignant Tumors in Children – ***Alvaro Martinez, Sarah Donaldson & Malcolm Bagshaw, Stanford Univ.***

Current results in treatment of childhood malignancy demonstrate prolongation of disease-free survival and expectations of increased cure rate. One of our tasks in children has become prevention of serious complications of treatment such as disturbances in growth and development, physiologic impairment of organ function, induction of genetic abnormalities, and secondary oncogenesis. This requires compulsive treatment planning and meticulous attention to the set-up techniques of radiotherapy.

Accurate localization of tumor volume is essential for allowing daily reproducibility of precise irradiation. This can be achieved with aid of immobilization devices such as casts and molds, three-point set-up techniques, careful beam shaping and collimation, and necessity for simulator films that document accuracy of technique. Dose distribution should be carefully calculated after contours have been taken through multiple levels of the area to be irradiated. Liberal use of filters, compensators, wedges, bolus, and moving or multiple stationary fields may be employed to minimize the volume of surrounding normal tissues included in the radiation field.

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-CM-67068

Title: *A–Section and development of promising folate antagonists*

Deadline: *Late December–early January*

Organizations having the necessary scientific and technical personnel and physical facilities to:

First, conduct an in vitro screen for folate antagonists to select promising anticancer agents; second, conduct appropriate pharmacological and biochemical studies directed toward establishment of unique properties which would justify a clinical trial of the selected drugs; third, in conjunction with possible early clinical trials, do ancillary pharmacological studies which would use, expand, and/or verify the previously acquired information on the drug.

Respondents will be required to select and propose, on the basis of experience and knowledge in the field, all test systems and experimental procedures which best satisfy the work requirements as outlined above. Assignment of agents for study as well as the time and form for reporting results will be made by the Drug Research & Development Program. Candidate organizations must have the capability to conduct all phases of the task and be able to demonstrate experience in each phase.

Proposals must include evidence for personnel with appropriate training and experience and physical facilities to conduct: (1) in vitro screening, (2) pharmacological and biochemical studies, and (3) the necessary ancillary pharmacological studies. Organizations must demonstrate competence and resources for the complete screening and studies of 40 to 75 drugs per year. Proposals will be invited for a three-year incrementally funded contract period.

Contract Specialist: D. Abbott
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