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HYPERTHERMIA, RADIATION ENHANCEMENT, NEW DRUGS OFFER MORE THERAPY ADVANCES, ASCO MEMBERS HEAR

Hyperthermia, fast neutron and pi meson radiotherapy, photoradiation, a radiosensitizer, and several new or developing drugs including

(Continued to page 2)

In Brief

CANCER ACT ACCELERATED PROGRESS, ACS PRESIDENT SAYS; SCANNERS SCAPEGOATS, EMI CHIEF CLAIMS

IMPROVED COMMUNICATION and cooperation between large referral institutions and the practitioner have made it "increasingly possible to have patients treated in their home communities," R. Wayne Rundles, president of the American Cancer Society, said at the annual ACS science writers seminar last week. Physicians and allied medical personnel have shown greater interest in and ability to treat cancer, "one of the most significant examples of the progress that we are beginning to make against cancer," Rundles said. Taking issue with Cancer Program critics, Rundles insisted that progress in cancer control has been accelerated since the National Cancer Act became law in 1971. . . . **NEW PUBLICATIONS:** *Cancer Nursing,* edited by Rachel Ayers, Memorial Hospital, NYC, which claims to be the first professional cancer nursing journal. Available, $18.50 per year ($15 prepublication price until June) U.S. and Canada, $25 elsewhere, from Masson Publishing, 14 E. 60th St., New York 10022. *Journal of Environmental Pathology & Toxicology,* edited by Myron Mehlman, Mobil Oil Corp. Available for $33 (plus $3 outside U.S.) per year for six issues from Pathotox Publishers, 2405 Bond St., Park Forest South, Ill. 60466. "Research on Children," proceedings of a conference in Houston last year, edited by Jan van Eys, M.D. Anderson. Available for $9.95 from University Park Press, 233 E. Redwood St., Baltimore 21202. "Pretesting in Cancer Communications," suggesting methods, examples and resources for improving cancer messages and materials. Available free from NCI Office of Cancer Communications, Bethesda, Md. 20014. . . . **COMPUTER TOMOGRAPHY** scanner manufacturer, EMI Medical Inc., claims that HEW guidelines to Health Systems Agencies are unreasonable and would severely restrict availability of the procedure for cancer and other patients. The guidelines would permit purchase of an additional CT scanner in a health planning area if the prospective purchaser can show that existing instruments in the area are baeing used for at least 2,500 "patient procedures" a year, and that the new unit has a potential for 2,500 procedures. A patient procedure was defined as the use of a scanner during a visit by an individual patient. EMI said the average patient receives more than one scan per visit, and that only 20% of the 1,000 CT scanners now in use meet the guidelines, although some are operated 70 hours a week. "The CT scanner has become the scapegoat in the war against rising health care costs," fumed EMI president Robert Hagglund.

PHASE I HYPERTHERMIA TRIALS PROMISE ADVANCES WITH DRUGS, RADIOTHERAPY

(Continued from page 1)

chlorozotocin and maytansine were the new treatment methods emphasized at the 14th annual meeting of the American Society of Clinical Oncology in Washington this week.

Hyperthermia drew the biggest crowd in the presentation of phase I and II trials papers (most of the meetings overflowed from the conference rooms into the halls as attendance exceeded ASCO expectations). Jane Marmor of Stanford and Joan Bull of NCI described early clinical trials they are conducting.

Marmor and colleagues Douglas Pounds and George Hahn used ultrasound to induce local hyperthermia, testing the safety and efficacy of ultrasound for that purpose. Tumors were held at 44-44.5 degrees centigrade for 30 minutes, with overlying skin cooled by a water jacket. Eighteen courses were administered to 16 patients. Eight of nine with squamous cell carcinoma of the head and neck had partial regressions. Three of seven with other histologies also responded. Regressions were short lived, although one lasted for eight months.

Five patients experienced pain during treatment. In all of those the tumor lay directly over bone, suggesting reflection of the ultrasonic energy. Four developed small painless superficial burns at the site of thermocouple insertion; these healed rapidly. Patients showed no skin damage despite extensive prior irradiation of the skin.

"We conclude that ultrasound can safely and effectively heat superficial tumor volumes," Marmor said. "Hyperthermia alone appears to have some activity in squamous cell carcinomas of the head and neck." However, the potential for hyperthermia lies primarily in combination with radiotherapy and chemotherapy. Marmor said trials were being planned in which tumors will be heated before and after irradiation. A number of other centers and the Radiation Therapy Oncology Group are developing protocols for treating skin lesions, some cancers of the rectum, pelvis and head and neck with hyperthermia and radiation.

Marmor said that 45 degrees is the highest her group has gone so far in heating tumors. "We probably can go higher, as long as we cool the skin."

Bull and her colleagues—D.E. Lees, W.H. Schuette, J. Whang-Peng, E.R. Atkinson, G. Bynum, R. Smith, J.S. Gottdiener, H. Gralnick and V.T. DeVita—reported on a phase I trial of whole body hyerthermia as treatment for metastatic cancer.

Hyperthermia is induced using a high flow water suit controlled by a microprocessor. Core body temperature is elevated by the insulated buildup of metabolic heat plus heat delivered via the warm water suit, which resembles an astronaut's space suit.

Fourteen patients were evaluated, age 18-61, with a variety of neoplasms. All tumors were metastatic with the exception of a chondrosarcoma which was unresectable.

No arrythmias occurred during the procedure. One patient developed bigeminy six hours after initial exposure for one hour at 40.5 degrees. This arrythmia lasted 12 hours but did not recur with subsequent treatments at higher temperatures. Neither this patient nor any of the others showed any evidence of cardiac damage. All patients required intravenous analgesia. The marked physiologic alterations that accompanied the high temperature required intense close monitoring. Toxicity included severe fatigue lasting several days in all 14 patients, weight loss in nine, nausea and vomiting in five, and diarrhea in four lasting less than 23 hours. Four patients were febrile for 36 hours after initial deffervescent. Five patients experienced a fall in systolic blood pressure after hyperthermia. This was easily managed by increased fluid replacement.

Four patients developed a peripheral neuropathy, although there was no other central nervous system dysfunction during or following treatment. All spontaneously recovered despite continued heat exposure.

Four of the 14 patients had a measurable tumor response: One had a 40% regression lasting 12 months of a colon carcinoma metastatic to the liver; one with metastatic melanoma had a mixed response with a 90% regression of spleen and soft tissue disease over 10 months; one had a 50% regression of a large abdominal mass lasting more than eight months; one had a 40% regression of a rectal carcinoma metastatic to the liver lasting four months.

Bull concluded that whole body hyperthermia to 41.8 degrees centigrade is a feasible and safe procedure if careful monitoring techniques are used. These studies are preliminary to protocols combining whole body hyperthermia with chemotherapy, Bull said. "But there are toxicities with heat alone. Combining it with drugs tremendously complicates it."

NCI is just starting a phase I trial with whole body hyperthermia and adriamycin.

Fast neutron radiation with and without 5-FU for locally advanced pancreatic and gastric adenocarcinoma

Reported by J. Macdonald, F. Smith, R. Smith, R. Ornitz, C. Rogers, P. Wolley, and P. Schein, Lombardi Cancer Research Center, Georgetown Univ. and George Washington Univ.

Fast neutron radiation has the theoretical advantage of requiring less tissue oxygenization than photons to achieve maximum cytotoxicity. This study tested the feasibility of delivering fast neutron radiation plus 5-FU for patients with locally advanced pancreatic and gastric adenocarcinoma. Eighteen patients received 1716 rads of 15 MEV fast neutron. 5-FU at 500 mg/m^2 or 375 mg/m^2 was ad-

ministered daily on the first three days of radiotherapy. Sixteen patients had moderate nausea and vomiting, three requiring hospitalization. Of 11 pancreatic patients, five achieved partial response with a median duration of six months. Median survival for all 11 was five months. The group concluded that upper abdominal treatment with fast neutrons plus the lower dose of 5-FU is well tolerated, and that a phase III trial is warranted.

Photoradiation in the treatment of recurrent breast carcinoma

Reported by Thomas Dougherty, Jerome Kaufman, Kenneth Weishaupt, and Abraham Goldfarb, Roswell Park.

Past clinical studies have shown that photoradiation has been highly effective in controlling a variety of cutaneous and subcutaneous neoplasms. "We find this new technique to be especially effective in eradicating local and regional chest wall disease which persists or recurs following conventional modalities such as chemotherapy, hormonal therapy and radiation therapy." Using a combination of hematoporphyrin, a light sensitive dye obtained from red blood cells, and local photo-activating visible light, complete or partial control was achieved in all nine patients treated. The regimen consisted of single or fractionated 20 minute exposures to red light, starting three to 10 days after injection with hematoporphyrin. Under these conditions, a high therapeutic ratio between tumor response and skin response can be achieved with complete tumor necrosis and regression usually occurring within one week and only mild erythema and edema of surrounding treated normal skin.

Each of the patients treated had failed or experienced disease recurrence with traditional treatment methods. Photosensitivity lasted for about four weeks in most of the patients but was controlled by minimizing exposure to sunlight. This method offers a new approach to treating chest wall diseases and appears not to be compromised by previous conventional treatments.

Negative pi-meson (pion) radiotherapy: an experiment in progress

Reported by Morton Kligerman, Univ. of New Mexico.

The goal of the project is to significantly increase the survival of patients with locally and regionally advanced cancers which are not currently well managed by any means. Negative pi-mesons are a charged subnuclear particle approximately one-seventh the mass of a neutron. These particles hold the neutrons and protons together in the nucleus. Because they are charged, they have a limited range in tissue and deposit most of their energy at the end of their travel where they are absorbed by the nuclei of carbon, nitrogen and oxygen. This causes instability of the nucleus with fission into large nuclear fragments and gamma rays. The result is that concentrated energy can be shaped to the tumor volume, and part of this energy is of a type that inhibits repair of sublethal damage to a greater extent than x-rays or gamma rays. Biological data to date support the clinical impression, on 49 cases with 95 tumors followed for six-12 months, that a therapeutic gain may result as compared with conventional radiation. Phase I and some Phase II studies are in progress. Areas of interest are gliomas, stage III and Stage IV head and neck tumors, superior sulcus tumors, esophagus, stomach, pancreas, and locally advanced bladder, uterine, rectal and prostate cancers.

Kligerman said he feels a 200-300% increase in survival may be possible with pi mesons, and that combination chemotherapy will be necessary with advanced disease patients. To date, he has observed complete response in 77% of treated patients, and partial response in 22%, "and the maximum doses are still to be reached. So far we've seen a lot of tumor response, and little normal tissue response."

Kligerman uses a machine at Los Alamos designed for physics research. He was asked how much it costs to treat patients in his studies. "From $24,000 to $35,000 each, when we are fully operational, which is comparable to chemotherapy."

That brought a reaction from Franco Muggia, who heads the Cancer Therapy Evaluation Program in NCI's Div. of Cancer Treatment.

"For $24,000, we treat 100 patients with chemotherapy," Muggia said.

Kligerman said a dedicated pion machine, used 24 hours a day, would bring the cost down to about the same as conventional radiation.

Maytansine: A phase I-II study

Reported by R.H. Blum, B.K. Wittenberg, G.P. Canellos, R.J. Mayer, A.T. Skarin, J.J. Lokich, I.C. Henderson, and L.M. Parker, Harvard.

(Ed. note: This is the natural compound isolated by the late Morris Kupchan at the Univ. of Virginia. It received considerable notoriety a few years ago in the popular press which heightened interest among many clinicians. Although it is a very powerful drug, some NCI executives feel its potential has been overrated. The Harvard group felt otherwise.)

From March 1976 to October 1977, 89 patients were entered; 67 are evaluable for toxicity. Dose escalation from 0.001 to 0.8 mg/m^2 qdx5 q21d in 21 patients demonstrated that 0.5 mg/m^2 qdx5 was the maximally tolerated dose. Then a more convenient schedule of 2 mg/m^2 q21d which resulted in similar dose limiting toxicity was given to 32 patients (57 courses). GI toxicity (mild 24%, moderate 32%, severe 23% and 4% requiring hospitalization) was characterized by nausea, vomiting, abdominal pain, and diarrhea followed by constipation. Neurologic toxicity (mild 34%, moderate 13%, severe 4%) was

characterized by lethargy, dysphoria, and insomnia. Peripheral neuropathy was insignificant except in one patient who had a partially reversible quadraplegia. A decrease in performance status occurred in 69% of courses, 9% of which were transiently incapacitating. Minor changes in liver chemistries occurred in 29%, phlebitis 7%, mucositis 2% and alopecia 4%. Most toxic symptoms receded by day 21, but 45% of 43 evaluable patients had some evidence of cumulative toxicity.

The group emphasized that no myelosuppression was noted. Forty-one patients with measurable disease are evaluable for response. Two responses greater than 50% were seen, one with bladder cancer for two months, one with oat cell cancer for two months. Two minor responses were seen in breast cancer.

Given reversible and predictable toxicity without myelosuppression, and two early responses, further clinical trials are justified, the report said.

Abstracts of reports on three studies of chlorozotocin, on a phase I trial of the radiosensitizer misonidazole, on a new anthracyclin derivative, and on 6-diazo-5-oxo-L-norleucine will be published next week in ***The Cancer Letter.***

ABSTRACTS OF OUTSTANDING PAPERS PRESENTED AT ANNUAL ASCO MEETING

The American Society of Clinical Oncology annual meeting program committee designated 22 papers presented at the meeting as outstanding. Abstracts of some of those papers follow here. Others were incorporated in the article starting on page 1, and still others will appear in following issues of ***The Cancer Letter.***

COMBINATION CHEMOTHERAPY OF DISSEMINATED TESTICULAR CARCINOMA WITH CIS-DIAMMINE-DICHLOROPLATINUM, VINBLASTINE, AND BLEOMYCIN (PVB): AN UPDATE – Lawrence Einhorn, Indian Univ. Medical Center

Fifty patients with disseminated testicular carcinoma were treated with PVB as previously described (ASCO 17: 240, 1976). Three patients died of progressive disease within one week of PVB, leaving 47 evaluable patients. Median followup was 20 months (range 13-38 months). Toxicity consisted primarily of nausea, vomiting, alopecia, stomatitis, myalgias, and meylosuppression, with the most severe and prolonged myelosuppression seen in patients with prior radiotherapy.

Only one patient had clinically significant bleomycin-induced pulmonary fibrosis. Four patients had severe nephrotoxicity (serum creatinine greater than 3 mg%) early in this study; however, in the past 18 months, all patients have routinely received saline hydration, preventing nephrotoxicity. Mannitol diuresis was not employed. There were 4 deaths while patients were in complete remission (C.R.); however, only 2 of these were clearly drug-related deaths. There have not been any drug-related deaths with PVB the past 2½ years. There were 33 of 47 C.R. (70%) and 14 partial remissions (P.R.). Five P.R.'s were rendered disease-free (NED) following surgical removal of residual disease; thus 38 patients (81%) achieved an NED status. The median duration for the other 9 P.R.'s was 11 months (range 4-30$^+$ months), with three patients remaining in P.R. at 16$^+$, 22$^+$, and 30$^+$ months. Thirty-four patients (72%) remain alive, and 29 (62%) patients remain NED with a minimal followup of 13 months. Eight patients had prior radiotherapy and 20 prior chemotherapy, including eight patients with actinomycin-D chemoprophylaxis.

Prior radiotherapy or prior chemotherapy for metastatic disease conferred an unfavorable prognosis for prolonged survival.

DETERMINATION OF THE GROWTH FRACTION (GF) OF HUMAN MYELOMA CELLS AT VARIOUS STAGES OF DISEASE – B. Drewinko and R. Alexanian, M.D. Anderson Hospital

Greater reductions of tumor mass load in patients with multiple myeloma may result from therapeutic strategies that are based on a better knowledge of growth kinetics. We have previously shown that the labeling index of myeloma cells remain unchanged when tumor mass is reduced and that the cells of relapsing patients have different biological properties than the cells present before melphalan-prednisone therapy. This study investigated the growth fraction of myeloma cells at various disease stages using continuous IV infusions of tritiated thymidine. We studied 11 patients on 13 occasions (3 untreated, 2 unresponsive, 4 in remission and 4 in relapse). All untreated and unresponsive patients had a GF, defined by the maximum percentage of labeled cells in marrow aspirates, of less than 1%. Two patients, with a response defined by a 75% reduction of myeloma protein, had similar values, while 2 others had GF of 4 and 8% respectively. These relapsing patients, with the most rapid tumor doubling times, had a GF ranging from 20 to 47%. The plasma cell generation time for all of these patients was 8 days and the calculated intrinsic cell loss ranged from 47 to 83%.

These findings support our model for the growth kinetics of multiple myeloma which contends that the entire tumor mass issues from a small proportion of prliferating cells and that the growth kinetics of myeloma cells in relapsing patients differ from those in untreated and unresponsive patients. Therapeutic trials with cycle-active agents need further investigation in selected relapsing patients lifely to have a high growth fraction.

INCREASED SURVIVAL FOLLOWING ADJUVANT RADIATION THERAPY IN OVARIAN CARCINOMA STAGES I, II AND ASYMPTOMATIC III – Alon Dembo, Raymond Bush, Frank Beale, Helen Bean, Jack Pringle, and Jeremy Sturgeon, Princess Margaret Hospital, Toronto

Four hundred patients of all ages with invasive epithelial carcinoma of the ovary of all stages have been prospectively studied since 1971. Combinations of post-operative irradiation and chemotherapy were randomly assigned to patients staged at initial surgery and stratified by age, UICC stage and histologic type and grade. Actuarial 5-year results are presented. Uncorrected surival for all patients studied is 42%, compared with 28% for patients treated between 1964-1966. This gain is largely attributable to improved therapy of patients with stages IB, II and III asymptomatic presentations, in whom 5-year actuarial survivals are 86, 58 and 27% respectively. Within these stages the ability to complete bilateral salpingo-oophorectomy and hysterectomy (BSOH) defines a subgroup of patients potentially curable by adjuvant post-operative radiotherapy (survival=61% compared with 23% when BSOH not completed).

For patients in whom BSOH was completed, 2250 rads pelvic irradiation plus 2250 rads abdominal strip irradiation resulted in significantly fewer (p less than 0.01) treatment failures (TF) in the upper abdomen (TF=0%) and significantly superior (p=0.03) survival rates (S=82%). Poorer results were obtained with either 4500 rads pelvic irradiation plus two years of chlorambucil chemotherapy (TF=27%, S=67%) or (in stages IB + II) pelvic irradiation alone (TF=23%, S=50%).

The opportunity for cure in post-operative patients may be lost if factors in addition to surgical stage do not form the basis for the therapeutic decision.

A RANDOMIZED PROSPECTIVE TRIAL COMPARING COMBINATION CHEMOTHERAPY (CRX) WITH TOTAL BODY IRRADIATION (TBI) PLUS CRX IN NON-HODGKINS LYMPHOMAS – H.D. Brereton, D.L. Longo, L.R. Kirkland, R.E. Johnson, R.C. Young and V.T. DeVita, NCI

Both TBI and CRX utilizing cyclophosphamide, vincristine and prednisone (CVP) or cyclophosphamide, vincristine, procarbazine and

prednisone (C-MOPP) are useful in the treatment of non-Hodgkins lymphoma (NHL). This trial was established to compare the efficacy of CVP/C-MOPP with CVP/C-MOPP plus TBI in establishing durable remissions in patients with stage II, III or IV lymphocytic lymphoma, nodular or diffuse, or stage II, III or IV nodular mixed or nodular histiocytic NHL.

Pretreatment staging procedures included lymphangiography, liver and bone scans, chest tomography, bilateral bone marrow aspirate and biopsy; liver biopsy and peritoneoscopy with liver biopsy when indicated. Patients were stratified according to stage and histologic subtype and randomly assigned to treatment. Nineteen patients were treated with CRX and 20 patients were treated with CRX-TBI. The latter group received TBI first (100 R in 10 fractions over 12 days). CRX was then delayed 8 weeks in this group to allow recovery from the myelosuppressive effects of TBI. The CRX in both arms of the study was CVP for patients with lymphocytic lymphoma and C-MOPP for patients with mixed or histiocytic lymphoma.

Complete remissions were documented by repeating previously abnormal x-rays, scans and biopsies as well as by resolution of all palpable disease. A complete remission (CR) was achieved in 78% of patients receiving CRX alone and 80% receiving CRX-TBI. Actuarial survival (greater than 80% at 3 years), disease free survival and treatment related toxicity were comparable for both groups of patients.

Despite the efficacy of each treatment modality alone, the combination of CRX and TBI does not improve the remission rate, nor does it appear to improve patient survival or disease free survival.

DEFINITIVE RADIATION THERAPY FOR STAGES I & II CARCINOMA OF THE BREAST – Jay Harris, Martin Levene, Samuel Hellman and Eric Weber, Joint Center for Radiation Therapy, Harvard

Between July 1, 1968 and Dec. 31, 1975, 80 patients with UICC stage I or II carcinoma of the breast were treated by definitive radiation therapy following biopsy. In all cases, pathology revealed invasive carcinoma, 4 patients had bilateral breast cancers for a total of 84 breasts treated. The median followup was 41 months with a range of 13 to 88 months. Five-year survival was 88% and 72% for stages I and II respectively while relapse-free survival at five years was 91% and 56%. None of the 28 stage I breast cancers recurred locally, and only one of the 56 stage II cancers treated recurred locally. A cosmetic evaluation was performed on 29 of the 46 patients living without disease. Sixty-six percent of the treated breasts were judged good or excellent by physician evaluation while patients judged the result good or excellent in 81%.

Only one complication of therapy required hospitalization. This occurred in a patient with bilateral breast cancer treated with a non-standard field arrangement who developed radiation pericarditis. Other complication included rib fractures (8 patients), pulmonary reactions consisting of cough and shortness of breath (3 patients) and pleural effusion (1 patient).

Surgical and radiotherapeutic expertise is required for good cosmetic results. The surgery should remove gross disease without a wide local incision. Circumareolar incisions, when possible, are preferred. Radiation therapy should be done using supervoltage equipment, without bolus, and with compensators to give good dose homogeneity. Total dose should not exceed 5000 rad given at 200 rad/day. If further dose to the primary tumor area is required, it should be given by interstitial implant.

These results demonstrate that radiation therapy can achieve local control and maintain a good cosmetic result.

ADJUVANT CHEMOIMMUNOTHERAPY OF STAGE IV (NED) BREAST CANCER – AN UPDATE – Charles Tashima, Aman Buzdar, George J Blumenschein, and Jordan Gutterman, M.D. Anderson Hospital

Fifty five breast cancer patients with no clinical evidence of disease (NED) following resection and/or irradiation of first metastatic recurrence were treated with combination chemoimmunotherapy consisting of 5-FU 400 mg/m^2 Day 1 and 8, adriamycin 40 mg/m^2 IV Day 1, cyclophosphamide 400 mg/m^2 IV Day 1 and Connaught BCG by scarification Day 9, 16 and 23 of a 28 day cycle (FAC-BCG). Adriamycin was discontinued at 450 mg/m^2 and substituted by methotrexate 30 mg/m^2 IM Day 1 and 8 for a total duration of 2 years.

The treated sites were chest wall in 30, supraclavicular nodes in 9, bone in 6, axillary nodes in 5, and 5 others. Historical controls consisted of 67 comparable patients with similar sites of first relapse, which were treated by surgery and/or radiation therapy, and followed without any systemic chemotherapy or hormonal treatment. The FAC-BCG patients, entered into protocol between January 1974 and October 1976, have now reached a median followup time of 27 months. Eighteen of 55 treated patients (33%) have developed metastases as compared to 57 of 67 controls (85%) (P less than 0.01). The median interval to second recurrence is 9 months for controls and in excess of 24 months for treated patients (P less than 0.01). At 48 months the survival rate is 84% for FAC-BCG patients and 50% for controls (P=0.04).

Update analysis continues to demonstrate the efficacy of intensive chemoimmunotherapy in prolonging disease-free interval and survival of stage IV breast cancer patients following local therapy of isolated recurrence.

STEROID HORMONE RECEPTORS IN HUMAN BREAST CANCER – J.C. Allegra, M.E. Lippman, E.B. Thompson, R. Simon, A. Barlock, L. Green, K. Huff, S. Aitken, M. Do, and R. Warren, NCI and Howard Univ. Cancer Research Center

Steroid hormone receptors (R) were determined in 142 female patients (Pts) with breast cancer. About 2/3 of these assays were performed on metastatic lesions. The frequencies of R positivities were: Estrogen Receptor (ER), 44%; Orogesterone Receptor (PR), 48%; Androgen Receptor (AR), 34%; Glucocorticoid Receptor (GR), 52%. The frequency of each R was independent of histology, nodal status, age, disease extent, and type of tissue assayed. PR and GR were positively associated with the presence of ER. AR was only weakly associated with the presence of ER. The presence of R and the results of therapy were evaluated. Fifty-three Pts underwent hormonal manipulation. ER+ Pts responded objectively 66% while ER– only responded 18% (p less than .01). The presence of PR or AR did not increase this predictive index; however, those Pts who were ER+ GR+ had a response rate of 90%.

Responders who were ER+ tended to have a longer response duration than those who were ER–. Chemotherapy correlations with ER were surprising. Pts who were ER– responded objectively 61% while ER+ Pts responded at a rate of only 11% (p less than .01). There was no correlation between the R status and disease free interval or overall survival. The presence of AR or GR showed a significant correlation with survival from the institution of endocrine therapy (p=.03). The failure to observe a positive correlation between ER and survival may reflect the counterbalancing positive and negative correlations of ER with hormonal and chemotherapy response respectively, since responses to either could be expected to prolong survival.

Analysis of multiple classes of R may delineate biologically important subsets of human breast cancer.

RANDOMIZED TRIAL OF LEVAMISOLE IN PATIENTS WITH SQUAMOUS CANCER OF HEAD AND NECK – Harold Wanebo, Elias Hilal, Elliot Strong, Herbert Oettgen, Carol Pinsky, Memorial Sloan-Kettering Cancer Center

Patients with squamous cancer of the head and neck have suppressed cellular immune function even when the disease is localized. Within stages, immunodeficiency is associated with high recurrence rates.

A randomized trial was initiated to compare the effects of adjuvant therapy with an immunopotentiator levamisole versus placebo in patients after complete resection. Patients were stratified as to site (oral cavity, pharynx, larynx), stage, and disease status at time of surgery (primary or recurrent). Of 54 patients randomized, 48 were evaluable; 9 of these had recurrent disease and 39 were treated for primary cancer. Of the latter 13 were stage I and II and 26 were stage III. Adjuvant radiation was given in 11 of 18 in the levamisole group and 12 of 21 in the placebo group. DNCB reactivity was also similar: 13/18 and 14/21 were DNCB-positive in the levamisole and placebo groups, respectively.

There was a significant reduction in recurrence rate in the primary disease group receiving levamisole, but no difference in those treated for recurrent disease. The estimated median time to recurrence was 9 months in 21 patients receiving placebo and has not yet been reached in the 18 patients receiving levamisole. At 12 months the estimated proportion free of disease was 34% in the placebo group vs. 82% in the levamisole group. A comparison of the recurrence distribution shows that the patients receiving levamisole do better than those receiving placebo (p less than 0.025). These preliminary results suggest benefit of levamisole as adjuvant treatment in patients with primary operable cancer of the head and neck.

MOPP VS MOPP PLUS ABVD IN STAGE IV HODGKIN'S DISEASE – G. Bonadonna, V. Fossati, and M. De Lena, Istituto Nazionale Tumori, Milan

MOPP induces CR in 70-80% of patients with advanced Hodgkin's disease. However, only about 50% achieve cure. ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) was found to yield a comparable incidence of CR as MOPP. ABVD also produced CR in 61% of MOPP resistant patients. Therefore, the attempt to increase the duration of disease free survival by alternating two non cross resistant combinations appears logical.

From November 1974 to March 1977, a total of 39 consecutive patients with proven extranodal extention were randomly allocated to receive either 12 cycles of MOPP (17 cases) or 6 cycles of MOPP monthly alternated with 6 cycles of ABVD (22 cases). Stratification included histologic subtype, prior RT, A or B symptoms. The comparative response after a minimum of 6 cycles in the absence of progressive disease was as follows:

	MOPP (%)	MOPP + ABVD (%)
Progression	35	0
Improvement	0	9
CR (pathologic)	53	55
CR plus PR	65	91

At the time of this abstract, only 1 patient is still on treatment and responding to MOPP compared to 13 of MOPP + ABVD group. Duration of CR and overall survival are reported below (data are in percent):

	1 yr		2 yrs	
	CR	Survival	CR	Survival
MOPP	88	100	65	90
MOPP + ABVD	100	100	100	100

Sequential therapy was no more toxic than MOPP. Although a long term analysis is required to confirm the initial findings, MOPP + ABVD seems to improve the response and the duration of CR.

STUDY OF LEUKEMIA BIOLOGY NEEDED TO IMPROVE TREATMENT, PINKEL SAYS

Acute lymphocytic leukemia in children is the first common cancer to be cured by chemotherapy, "but we're still losing half of our patients because of the disease's resistance to treatment," Donald Pinkel said this week when he delivered the annual David A. Karnofsky Memorial Lecture at the meeting of the American Society of Clinical Oncology in Washington.

The half who are being cured are those who receive the optimal treatment in the most advanced facilities. "Most children with the disease around the world do not benefit from these advances," said Pinkel, now at Milwaukee Children's Hospital. "The treatment is too complex and is not accessible to them.

"The challenge we face is to solve the problem of resistant leukemia by investigating the biology of leukemia as it occurs in children, and then develop effective treatment that is simple and safe."

Pinkel, who for several years was medical director of St. Jude Children's Hospital, discussed studies at St. Jude's which involved attempts to improve on treatment that is producing long term remissions in 50% or more of ALL patients. Complete remission is the initial treatment objective, through chemotherapy. Prophylatic irradiation of the central nervous system is then administered, followed by remission maintenance chemotherapy.

The fact that this regimen, in various combinations of drugs, produces 50% long term remissions suggests "there is one group of children in which we can't control the disease, another group in which control is achieved but relapse occurs, and another group in which we can eradicate the disease," Pinkel said.

"What about the other half? Why can't we save them?" Pinkel asked. The major reason, he suggested, is the acquired resistance of leukemia to treatment. "There are several classical ways to try to overcome this resistance:"

1. Increase dosage. He cited studies which demonstrated that acquired resistance cannot be overcome by higher doses.

2. Administration of high doses of drugs in the early weeks of remission. But again, studies indicated there is no significant benefit with this method compared with standard doses.

3. Intensive chemotherapy early in remission with agents not used to induce remission. This also did not offer any advantage.

4. Addition of more drugs to the regimen. Comparing single drug with two, three and four drug combinations, the results turned out to be the same, Pinkel said. "You can't assume that more drugs are better, or that higher doses are better."

So what is next?

"We must restudy the disease, learn more about the biology of leukemia. If we gain a better understanding of it, we can improve the treatment."

As examples, Pinkel said that studies of the biology of ALL in the last five years reveal that there is a relationship between the types of cell surface markers and responsiveness to therapy—"one type will be responsive to cyclophosphamide, another to methotrexate. One type of cell might have more receptors for certain drugs, with better absorption."

KENNEDY ASKS ASCO MEMBERS TO HELP LOBBY FOR HIGH TAR/NICOTINE TAX

"It's important that all of you who devote your lives to dealing with cancer help in the effort to alert other members of Congress of the need to deal with the health threat caused by tobacco," Sen. Edward Kennedy told ASCO members.

Speaking informally following the annual ASCO dinner, Kennedy said, "You can't be warm about cancer research and cold to the problem of smoking." He has joined with 31 other senators in sponsoring

a bill to increase taxes on high tar and nicotine cigarettes, Kennedy said. "That means there are more than 60 members of the Senate who need to be educated. To bring sanity to this issue, we need your support. I don't want you coming in asking for more money for cancer research and then turning your back on the tobacco problem."

Four years ago, Kennedy's son, Teddy, was diagnosed with osteogenic sarcoma in one leg. After amputation, he received chemotherapy in one of the then new adjuvant regimens.

"Teddy is doing magnificently well," Kennedy said. "Our family is forever indebted to you who through your genius made his life and progress possible."

Kennedy later told ***The Cancer Letter*** that he intended to remain as chairman of the Senate Health Subcommittee when he becomes chairman of the Judiciary Committee next year. "I wouldn't give up that pleasure," he said. He will take over Judiciary with the retirement of Sen. James Eastland of Mississippi, who will not run for reelection.

CONTRACT AWARDS

Title: Investigation of a slit scan technique as a basis for an automated prescreening system for cancer detection in cytology, continuation
Contractor: Univ. of Rochester, $357,062

Title: Provide data research analyses for breast cancer treatment program, continuation
Contractor: EG&G/Mason Research Institute, $225,000.

Title: Breast cancer detection demonstration project, renewal
Contractor: St. Vincent's Medical Center, Jacksonville, Fla., $270,000.

Title: Clinical oncology program
Contractor: Valley View Hospital, Ada, Okla., $250,582.

Title: Acquisition of tumor specimens for virus studies, continuation
Contractor: Memorial Hospital, $242,700.

Title: Studies on the Epstein Barr virus and its association with nasopharyngeal carcinoma
Contractor: Ohio State Univ., $489,260

Title: Cultivation of mammary tumor viruses, continuation
Contractor: Univ. of California (Davis), $179,452.

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-85624-50

Title: *Identification of heterozygous carriers of DNA repair defects*
Deadline: *May 13*

Chief objective is the development of suitable techniques whereby carriers or heterozygous individuals may be identified in the general population. Such techniques might depend upon isolation and characterization of the enzymes and other important molecules involved in DNA repair. Alternatively the isolation of mutant cell lines, human or otherwise, might be considered as a useful approach to the problem. Other types of experiments which serve to further the objectives of this project may be suggested by the proposers and will be given full consideration.

A 39-month contract is anticipated for effective pursuit of this project.

RFP NO1-CP-85623-50

Title: *Isolation and purification of human polycyclic hydrocarbons metabolizing enzymes and the production of antisera to the pure enzymes*
Deadline: *May 13*

NCI is interested in establishing a contract for a project which consists of the following two tasks: 1. To isolate, purify and characterize enzymes involved in polycyclic hydrocarbon metabolism from human sources. 2. To prepare monospecific antibodies to these enzymes.

A 38 month contract is anticipated in the effective pursuit of this project.

Contract Specialist for above 2 RFPs: J. McHugh
Carcinogenesis
301-427-7574

RFP NO1-CP-85617-62(088)

Title: *Evaluation of the transformation assay using C3H 10T½ cells for use in screening chemicals for carcinogenic potential*
Deadline: *June 7*

NCI is interested in evaluating and determining the usefulness and reliability of an in vitro transformation assay using C3H 10T½ cells for routine use, as one of a battery of short-term assays, in the initial determination of the carcinogenic potential of chemical compounds. The government estimates that approximately three professional man-years of effort

for three years is required for this project.

Contract Specialist: Dorothy Britton
Carcinogenesis
301-427-7914

RFP NO1-CP-85621-69

Title: *In vivo nutritional and metabolic studies to evaluate dietary induction of potential mutagenic/carcinogenic substances in humans*

Deadline: *June 12*

To determine whether existing techniques for the conduct of metabolism studies are adequate or can be adapted for use in human experiments to evaluate the role of dietary factors or in vivo mutagen/carcinogen production. In addition, this project will use the proposed standardized procedures to conduct metabolic studies using a variety of diets and several distinct population groups. This project will be an observational clinical study conducted on either an inpatient or outpatient basis.

The principal investigator and project staff will also be required to participate in the development of a protocol for the assay of biological samples to be developed by a separate contractor. This study will be conducted in phases. Phase I will consist of a literature review, identification of problem areas, and the subsequent development of an experimental protocol to answer the identified problems. Phase II will involve the conduct of experiments and studies to solve the logistical and technical problems identified in phase I and the development of a protocol and operations manual for the conduct of initial studies. Phase III will involve the conduct of the metabolism study and the final development and documentation of standard operating procedures for the conduct of metabolic studies in humans.

RFP NO1-CP-85619-69

Title: *Interactions of diet/nutrition and the use of genetically distinct animal strains in carcinogenesis studies*

Deadline: *June 13*

Evaluate the effect of diet on incidence of spontaneous and/or chemically induced tumors in specific strains of mice. The project will entail using two defined dietary regimens in combination with specific carcinogenic agents to compare effect of a semipurified diet and a natural product diet on carcinogenesis. The project will be coordinated with other DNCP projects since it has implications for other nutrition related projects.

The contractor will be required to adopt and follow a common protocol developed in consultation with the project officer. The final protocol must be approved by the project officer before initiation of the experiments. The experiment will be a fractorially designed study of 40 experimental treatments (2 diets X 5 carcinogens X 4 strains of mice). The experimental diets will be evaluated in long term feeding trials. A minimum of 50 mice (25 male and 25 female) per treatment will be tested.

RFP NO1-CP-85620-69

Title: *Validation and standardization of in vitro techniques to assess the effect of diet/nutrition on the mutagenic/carcinogenic potential of human secretions and excretions*

Deadline: *June 9*

Establish techniques for evaluating the mutagenic/-carcinogenic potential of human bodily secretions and excretions along with dietary components, which involves the following: To identify techniques for identifyong and separating suspected mutagens/carcinogens groups from bodily secretions and excretions; to identify techniques for quantitating the mutagenic/carcinogenic potential of various bodily secretions and excretions and their component parts; to identify and quantitate the mutagen/carcinogen groups present in the food consumed by experimental subjects; to assess applicability of these techniques for large screening; to validate the above techiques; to determine mean values and ranges (by age and sex) for subjects consuming certain diets and to recommend standardized methodoligies and procedures.

Contract Specialist for above 3 RFPs: Linda Waring
Carcinogenesis
301-427-7575

RFP WA 78-C243

Title: *Cytologic studies in areas with atypical environmental radon concentrations*

Deadline: *April 15*

Establish and complete an epidemiologic study in an area of high environmental radon concentrations and an area of low radon concentrations, examining sputum cytopathology and peripheral lymphocyte chromosome aberrations in subjects from each area.

If your organization has been advised that an EPA "RFP list" number has been assigned to the organization's address, your letter or telegram must include the assigned number. Telephone requests will not be honored.

Environmental Protection Agency
Headquarters Contract Operations
Contract Preparation Unit
Contracts Support Section
Crystal Mall No. 2, Room 708 (PM-214-C)
Washington, DC 20460

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