THE CANCER LETTER

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RAUSCHER SUMMARIZES CRITICISM OF COOPERATIVE GROUPS; CHANGES TO AWAIT MAY 22-24 CONFERENCE

Decisions involving the possible transfer of the Clinical Cooperative Groups program from NCI's Div. of Research Resources & Centers to the Div. of Cancer Treatment, and other significant changes in the operation and organization of the program will not be made until after the Potomac Conference May 22-24. NCI staff and group representatives will discuss criticism CCG has received, along with various suggestions for improving the program.

The Potomac Conference is open, and is scheduled to start at 8:30

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In Brief

THREE MORE COMPREHENSIVE CENTERS MAY BE NAMED; HAWAII, CLEVELAND, OHIO STATE LEAD LIST OF 10

THREE ADDITIONAL comprehensive cancer centers may be "identified" (recognized, designated, whatever) by NCI next month, either just prior to or at the June meeting of the National Cancer Advisory Board. The three will be selected from 10 that have submitted applications. Those at the top of the list at this time (but with no assurances they will be the successful ones) are the applications from Hawaii and two from Ohio—Cleveland and Ohio State Univ. The pressure will really start to build on Director Frank Rauscher after the three June selections are announced. That will put the number of comprehensive centers at 20, the most the White House wants to permit. Congress is insisting that NCI should be free to name as many as the cancer program requires, and Rauscher and the NCAB say that could be up to 30. This is another fight the White House is destined to lose, but Rauscher could avoid a confrontation by not adding more comprehensive centers until after the 1976 election—depending on who wins. . . . **RUMORS ARE** circulating at NCI that Rauscher will resign soon because of Administration policies—the ridiculous budget request, personnel ceiling, various attempts to ignore the intent of Congress as spelled out in the National Cancer Act. Don't believe them: when and if Rauscher does leave, he will do so only to assure the financial security of his family. Some of the offers he's received look very good compared with his government salary, frozen at $36,000 since 1969. Rauscher enjoys his job, including even his difficulties with the Office of Management & Budget, and will stay as long as he feels he can afford to—but that won't be indefinitely. . . . **INTERFERON** production may be stepped up by NCI. Labs in Finland and Switzerland are producing the material being used in clinical trials in Sweden. The Swedish tests indicate interferon is successful against osteogenic sarcoma. Whether it can equal the results obtained in the U.S. with methotrexate followed by citrovorum rescue remains to be seen. Both methods are used as adjuvant therapy following surgery; interferon would be less toxic than MTX.

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D'ANGIO AGREES CLINICAL RESEARCH AT NCI "RATHER CONFUSING PATTERN"

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a.m. each day, in Building 31 Conference Room 6 at NIH. The agenda includes reports by NCI division directors and other NCI executives whose programs include clinical research; workshops on CCG organization and operation—categorization and finances, group characteristics, intergroup studies; data standardization, accumulation, processing and analysis; and education, communication, and quality control.

NCI Director Frank Rauscher has considered moving the cooperative groups to DCT, in line with his decision to transfer the Surgery and Radiotherapy Branches from the Div. of Biology & Diagnosis to DCT.

But Rauscher now is leaning toward leaving the cooperative groups in DRR&C and handling the problems of coordination and communication through a new office that would monitor all NCI extramural research (*The Cancer Letter,* May 2). Whatever Rauscher's decision, it is almost certain that some changes will be made in the structure and operation of the cooperative groups.

Thomas King, DRR&C director, said he hopes the Potomac Conference will produce the answer to this question: "How can the cooperative groups help coordinate the therapeutic programs within our division and help those in the other divisions?

"I hope we can come up with a series of recommendations, including one for self-evaluation of the cooperative groups."

King said one suggestion that might be made to Rauscher is that a blue-ribbon panel be established, one with no allegiance to any NCI division, to objectively advise him on the problem.

Rauscher expressed some of the criticism and suggestions for improvement in an exchange of letters with Giulio D'Angio, Sloan-Kettering, who is chairman of the Cancer Clinical Investigation Review Committee, which advises NCI on the CCG program.

"Some months ago I was confronted with a verbal and written report (and consensus discussion) that was moderately to highly critical of this program," Rauscher wrote. "The concerns and criticisms had to do with the review process, geographic distribution, possible competition for patients, currency and optimacy of protocols, duplication and unnecessary duplication, reporting, responsiveness (groups and NCI), accountability to the public, physician certification and the like. . . . "

Rauscher suggested the questions that need to be resolved:

"Should all or some of the groups be a part of the Div. of Cancer Treatment? Why? Why not? In other words, I'm not convinced that NCI is doing the best job in helping the groups to do even better than they have.

"Are there too many groups? Too few? Too much or too little money? Should we have a better five-year projection? Do we have the best geographic distribution? Is this important? Are some groups demonstrably better than others? Should the less-than-best groups be phased out, improved, phased into the best groups?

"What is (and what should be) coordination among multiple programs in specific geographic areas regarding clinical cooperative groups, task force projects, cancer control projects, projects supported by DCT and DCB&D via contracts, Breast Cancer Task Force, and projects supported by American Cancer Society and Regional Medical Programs?"

Rauscher emphasized that he would "rely very heavily" on advice from CCIRC members in reaching decisions on those matters.

D'Angio responded by saying, "I agree thoroughly that those are the issues that must be resolved." He offered two suggestions:

- Attempt to "coordinate the rather confusing pattern of programs and projects at NCI that involve clinical investigation." As an interim measure, at least, this could be through a "central coordinating panel" made up of senior executives from the NCI divisions, with coordination achieved through liaison subcommittees.
- Make more effective use of the cooperative group chairmen. "They constitute a valuable resource that is not being used to full advantage. The chairmen are individuals who understand the strengths and weaknesses of the Cooperative Clinical Trials mechanism. They therefore are in an excellent position to give guidance regarding the broad question of clinical investigations, and in providing programmatic direction."

RAUSCHER EXPLAINS TREATMENT CHANGES IN MEMO TO NCI STAFF

The decision to combine all major research treatment modalities at NCI within the Div. of Cancer Treatment, removing the Clinical Director, Surgery and Radiotherapy Branches from the Div. of Biology & Diagnosis, actually stirred up more furor among various constituencies around the country than it did within NCI, Director Frank Rauscher told *The Cancer Letter.*

Former DB&D Director Nathaniel Berlin and the division's Board of Scientific Counselors adamantly opposed the change. Some participants in the division's extensive contract research programs, along with others from the academic and scientific community, expressed their opposition in a torrent of letters and phone calls to Rauscher.

When Rauscher revealed more than a year ago that he was considering making the changes, he said it would be the toughest decision he would have to make and one that probably would be bitterly op-

posed whichever way the decision went.

Rauscher explained his reasons behind the decision in a memo to NCI executives. The memo follows (with limited editing):

"While I know there is good clinical collaboration among the divisions, I am persuaded that this could be even better and more efficient. This is especially important in terms of continuing inadequate numbers of positions and the over-workloads of people who now have these responsibilities.

"I believe this is one credible and justifiable way for NCI to underscore its belief and statements that the patient is best served by combined modality approaches to treatment. I am fully committed to encouraging the individual modalities to develop along their own intuitive lines. That is that none will be subjugated to any single modality.

"I have needed and will need, at upcoming OMB and congressional hearings, to justify our near desperate request for more positions and therefore to document that our people within the present ceiling can function to best advantage for a National Program and for their own interests in cancer research.

"It will also mean, as an example, that the director, DCT, will not have to use positions (now nonexistent), time, and energy to recruit professionals with the kind of surgical and radiologic competence needed on a day-to-day basis to sponsor and coordinate the most effective National Program in cancer treatment. All of us know the critical importance and difficulty of this issue in view of the scarcity of these kinds of people, at current workloads and salary levels, and in view of the fortunate fact that Steve Rosenberg and Ralph Johnson and their colleagues are the very kind of innovative investigators and practitioners that can make a coordinated treatment program go best.

"I am convinced that this must and can be done while at the same time preserving all research opportunities, time, funds, space, etc., to all persons involved in this move and to all others who seek to continue or to initiate collaborative activities.

"It will help me in that I will have to go to fewer people to be able to respond to the more than 20,000 inquiries we get per year on clinical activities from the public, Congress, Executive, Panel, Board, etc.

"It will help those who have the legal and moral mandate to develop a best possible National Program in cancer treatment research.

"It will also help the lay public and professionals in knowing better whom to contact at NCI for broad or specific information. Just one recurrent example: Whom does someone call to get the latest information on current funding and progress in treating colon cancer? Budget officer? Head of surgery? Director, DCT? NCI head of the task force? M.D. Anderson head of the task force? Head of radiotherapy? Head of grants? Of Contracts? Me? I know very well that this realignment will not solve all of these communication problems. But it will help a lot.

"I recognize that this decision will be unpopular with some. I've spent much time over nearly 12 months seeking advice and opinions. Now I ask for your support. And I ask for your continuing support of Dr. DeVita, DCT, who did not initiate this action and for Dr. Rabson, who so much has my confidence that I've asked him to lead the largest division within NCI. I fully recognize the long history of preeminent investigator excellence within the DB&D. No other people or units of this division will be transferred unless, of course, on their own initiative, with concurrence of the division director, and if within the best interests of the NCP.

"Drs. Rosenberg and Johnson have agreed to make this transfer and to do all they can to make it work well through strengthened intramural and national programs. I have given them my personal commitment and that of DCT that they will be encouraged to continue their intramural research efforts with full NCI support and that responsibilities to the National Program will be compatible with their interests on campus.

"I thank those who cautioned me against this decision and those who were aggressively supportive of this action and who advised me that it was well past time that this was done. As Director, I must try to assure that NCI is responsive to people here and to an expanding, visible, and accountable National Cancer Program."

NIAMDD SCIENTISTS FIND VIRUS GENE CAUSES, CONTINUES CANCER

Scientists at the National Institute of Arthritis, Metabolism & Digestive Diseases have reported findings that show a virus gene is needed not only to initiate the cancerous process in previously normal cells but must be continually present for the cancer cells to continue growing.

NCI Director Frank Rauscher, a virologist himself, said the work by Robert Martin, Janice Chou, Jesus Avila and Rein Saral is "terribly important and significant."

John Moloney, who heads NCI's virus cancer program, called the NIAMDD research so good that "I wish we had supported it. . . . It means that if you can remove or incapacitate the virus, you can remove the neoplasm."

The research provides solid evidence for the long-held belief that virus genes become incorporated into a normal cell's gene profile. They then direct abnormal reproduction of DNA.

The team's report, which appears in the March issue of the *Journal of Virology*, pinpoints at a molecular level the region of a virus which actually initiates and maintains a cancerous change.

The Martin team used the SV-40 virus in the experiments, concentrating on heat-sensitive mutant

viruses unable to grow above 33 degrees C.

SV-40's circular DNA is now known to consist of five regions–gene regions–termed A, B, C, BC, and D, according to the sequence in which they were identified. To determine the role of these various gene regions, Martin and colleagues studied events occurring when SV-40 viruses defective at different gene regions were exposed to high temperatures. They found that only the A mutants, unlike other SV-40 mutant viruses, did not cause a cancerous change when inoculated into hamster cells at 40° C. This was evidence that the A region was necessary to start the cancerous change, a phenomenon postulated by Peter Tegtmeyer of Case-Western Reserve in 1972.

In additional experiments, Martin and associates discovered that after SV-40's DNA was incorporated into the DNA of hamster cells, the A region was the only area of viral DNA whose functioning was essential to perpetuate the cancerous change.

The A region is thus marked as the key site of SV-40's ability to initiate viral DNA synthesis and to maintain malignant transformation of the next generation of cells.

The NIAMDD scientists propose that the expression of normal A gene function is not fully autonomous, but is determined by the place where it is incorporated into the cell's DNA. For example, if SV-40 is integrated into cellular DNA active only in the period immediately prior to the production of new cells, there would be insufficient time for the cancerous change to occur before cell division. By contrast, if the virus is integrated into cellular DNA that is active following cell division, it would be continually stimulated by the A gene it harbors to manufacture abnormal DNA, maintaining the cancerous state.

Rauscher said that the NIAMDD findings should be followed up with similar research using RNA viruses, since the SV-40 is not a naturally-occurring virus. "If the concept is true, then we can attack the inducer and continuer by engineering a drug to hit the virus rather than the DNA turnover," Rauscher said.

NINE SATURATION PROGRAM PLANNING CONTRACTS WILL BE AWARDED BY NCI

NCI's Div. of Cancer Control & Rehabilitation has selected nine proposals out of 33 applications submitted for the community-based cancer program, the so-called "saturation program." Announcements of the successful applicants will be made following completion of negotiations.

The staff is scheduled to make the final review May 12 of applications for the implementation contracts.

Of the 33 responses for the planning contract, 23 were selected for site visits. Each of the planning awards will be about $100,000 for direct costs.

Laurence Callan, associate director for community activities, said that some of the proposals were "super." Perhaps the single most important factor in rating the proposals was the degree of involvement they were able to achieve among various elements of their communities.

One community was so advanced, especially in the matter of cooperation, that Callan suggested they switch from planning to the implementation phase. The applicant declined, insisting his team needed further planning.

Callan said he was "disappointed" by the lack of understanding among some applicants on the need for "visibility" in the community and the requirement for involvement of a wide range of community resources in the program.

LUNG CANCER STUDIES SUPPORTED BY NCI, VA OUTLINED IN REPORTS TO ADVISORS

Bronchogenic carcinoma is the most common malignancy and the leading cause of death from cancer among American men. NCI supports a wide range of lung cancer studies, and the Veterans Administration, with a big patient population in the lung cancer high risk age group, also has a major program under way.

Stephen Carter, deputy director of NCI's Div. of Cancer Treatment, and George Higgins, chairman of the VA Surgical Adjuvant Group, presented reports on these studies to the DCT Board of Scientific Counselors.

Carter said that "there is a great deal of overlap in the studies and all are hampered by a lack of common definitions for patient input criteria, response criteria, and data reporting."

Higgins said, "The most promising approach appears to be multiple drug therapy possibly combined with immunotherapy."

DCT Director Vincent DeVita said, after hearing the reports, "What came across to me is the tremendous resource the Veterans Administration has to implement any findings we may make, with its big patient supply." DeVita said an overwhelming consideration in developing effective treatment for lung cancer is the total collapse of the host that usually ensues, "more so than for any other tumor. . . . It's time we devoted more effort to studying the reasons for host collapse."

Carter's report, with limited editing, follows:

The data in over 22,000 cases from 1955 to 1964 show that only 21% of patients could receive a surgical resection at the time of diagnosis. In this group the overall 5-year survival rate was 7% with an observed median survival time (MST) of .4 years. For 4,193 cases that were localized at diagnosis the 5-year survival was 24% with a 1.1 year MST. Unfortunately, the percentage of cases with localized disease at diagnosis has remained stable since 1940. In the period 1940-1949, 18% of cases were localized and from 1965-1969 the percentage remained exactly the same. During that time the percentage receiving surgery did increase from 11% to 27% and overall 3-

year survival for all cases rose from 6% to 11%. In cases of localized disease 3-year survival has increased from 17% in the 1940s to 39% in the period 1965-1969.

The situation is truly dismal in patients who are considered inoperable at the time of diagnosis. The VA Lung Cancer Study Group (VALCSG) has reported an analysis by extent of disease, as well as histologic type, in a series of inoperable patients who received only supportive therapy. Patients with tumor clinically confined to one hemithorax (i.e., within the confines of a single radiotherapy portal) were termed as having "limited" disease and all others as "extensive" disease. In 130 patients with limited disease the MST was 15.7 weeks from the time the patient was deemed inoperable, while in extensive disease the MST was 9.4 weeks.

Efforts to improve these dismal results by radiotherapy and chemotherapy have so far met with very limited success. Patients with limited disease may experience some improvement in survival from radiotherapy alone. A large-scale randomized study of radiation therapy vs. placebo by Roswit et al. showed that treated patients survived about 20% longer than untreated controls. The effect of radiotherapy on limited disease may be particularly true for the squamous cell types, with MST of 60 weeks in such patients vs. 25 weeks in a group receiving single-drug therapy in the most recent study of the VALCSG. However, other studies have failed to demonstrate improved survival, even in limited disease, for patients receiving radiotherapy.

Again, in the setting of clinically limited disease, there are conflicting reports with regard to whether combined radiotherapy and chemotherapy can improve survival. Durrant et al, in a randomized study, found no advantage for nitrogen mustard (NH_2) + radiotherapy over that gained using radiotherapy alone, chemotherapy alone, or no treatment until the development of symptoms. Host found no advantage in cyclophosphamide (CTX) + radiotherapy vs. radiotherapy alone in patients with epidermoid carcinoma. Hansen and Selawry, using radiotherapy $\pm$ HN_2 and methotrexate (MTX) as a 2-drug combination, reported MST of 30 weeks for radiotherapy alone in patients with limited squamous disease and 21 weeks in the combined therapy group. Samuels, however, in a selected population of patients with limited disease (21/27 with squamous tumors), recently reported striking results in patients who achieved measurable tumor regression. His protocol employed bleomycin (BM), vincristine (VCR) and MTX for a 3-week period, followed by split-course radiotherapy (3000 rads in 2 weeks, repeated in one month). Further courses of chemotherapy were given as tolerance permitted. Fifteen of 27 patients responded, including 5 with complete responses. The MST in the non-response group was 26 weeks; estimated MST for responders was 70 weeks.

Selawry has extensively reviewed the objective response rate in terms of cell type for single agent chemotherapy employing a wide range of drugs. This data shows that chemotherapy has produced a reasonable response rate against each cell type, with the small cell type being the most responsive. Unfortunately, this has not been translated into meaningful improvements in survival time. Presumably, the lack of survival gain is due to factors such as rapid development of resistance, drug toxicity and, perhaps most importantly, failure to affect a majority of patients favorably. In addition, it may be that the X-ray measurement of shrinkage that we use is not reflecting a very large tumor cell kill.

This . . . review will discuss the work of 10 groups (Lung Cancer Working Party, the two VA groups, and seven cooperative groups), but will not be encyclopedic concerning studies in the cancer centers or those supported by traditional project grants.

The LCWP has a series of protocols covering the major cell types and the various disease stages.

There are three studies in small cell carcinoma. For regional disease, Protocol 7221 compares the rate and duration of response using CCNU + CTX + MTX and chest irradiation (5000R) vs. the same treatment with "elective" brain irradiation (3000R). In Protocol 7222 for extensive disease the 3-drug chemotherapy alone is compared to the same chemotherapy + brain irradiation (3000R), chest irradiation (2000R), and abdominal irradiation (2000R). Protocol 7223 for progressive extensive disease compares hexamethylmelamine (HXM) alone and HXM + VCR + BM.

In epidermoid carcinoma extensive disease was covered by Protocol 7311 which compared "COMB" therapy (CTX, VCR, methyl CCNU, BM) to CTX alone. This study was recently replaced by a series of Phase II evaluations of new agents. For regional epidermoid disease the comparison in Protocol 7312 has been a short course of radiotherapy (2000R in 5 days, 3 weeks rest, 2000R in 5 days) vs. a long course (3000R in 3 weeks, 2 weeks rest, 2000R in two weeks). This will be replaced by another radiotherapy protocol which may involve the addition of immunotherapy. The protocol (7351) for resectable epidermoid disease, as well as resectable large cell and adenocarcinomas, is surgery alone vs. surgery + CCNU. In extensive adenocarcoma and large cell carcinoma, Protocol 7452 compares CCNU + CTX + MTX to adriamycin (ADM) + procarbazine (PCZ) with the regimens crossing over upon disease progression.

The VALCSG recently started Protocol 15. Their protocols have involved treatment of "limited disease", which could be considered regional disease, and "extensive disease" which is disseminated disease.

The "limited disease" portion of Protocol 13 randomized patients between radiotherapy alone and radiotherapy + CCNU + hydroxyurea (HU). Analysis of all patients by therapy showed no important diff-

erence between the two treatments; major survival differences were not apparent. Further division of these groups by cell type led to relatively small numbers of patients in each treatment group. Continuation of this study is needed and is planned to provide sufficient numbers of patients so that meaningful conclusions can be drawn.

The "extensive disease" portion of Protocol 13 called for randomization to one of five treatment groups. One group was CTX (1,100 mg/m^2 IV every three weeks) as the standard for comparison. The other arms included CCNU, methyl CCNU, and combinations of CCNU + CTX with cross-overs to CCNU + HU at the end of 6 and 12 weeks, respectively. If all histologic types were taken together, survival figures for high and low performance status groups, by therapy, did not reveal important differences. Analysis of survival by histologic category, without regard to performance status, also did not show important differences. In one instance where a statistically significant difference was found, it was attributable, at least in part, to disproportionate numbers of patients in the low performance category. Analysis of survival by cell type and performance status can be done only in a preliminary way and further comment by the group has been deferred until all patients entered in this protocol can be evaluated. There does appear to be a trend, which is not yet statistically significant, toward longer survival in patients treated with the combination chemotherapy.

Protocol 14 of the VALCSG explored the relationship of survival to treatment with CTX + CCNU vs. CTX alone. In addition, combinations of CTX + ADM were evaluated.

Protocol 15 eschews chemotherapy completely and is a cooperative investigation of radiotherapy in the treatment of locally advanced (inoperable) carcinoma of the lung. Patients are randomized to one or two dose-time regimens for treatment of the primary tumor and mediastinal lymph nodes. Within each dose-time regimen half the patients will be randomized to receive prophylactic irradiation of the brain.

The VASAG protocols are for adjuvant therapy following resection in male patients. Patient selection involves those with no microscopic evidence of residual disease and randomization and treatment are started no later than the 30th postoperative day. Treatment is either CCNU and HU in repeated courses or no drug.

The Eastern Cooperative Oncology Group has protocols for both local and disseminated disease with the latter studies individualized to some degree by cell type.

In local disease of all cell types, Protocol 3573 attempts to evaluated the ability of BCG to extend the disease-free interval after surgery in patients having minimal residual tumor mass who are, however, at high risk. The study will also assess the effect of repeated BCG vaccination on various parameters of both in vitro and in vivo immune function.

The group has evaluated two dose levels of ADM vs. a CTX control in disseminated squamous cell and large cell anaplastic carcinoma. At progression the ADM-treated patients were crossed over to either cytoxan alone or CTX + cis-platinum diamminedichloride, while the CTX-treated group were crossed to the two dose levels of ADM. This study has just been revised to replace the high dose ADM with an arm combining ADM + CTX.

In small cell carcinoma the ECOG showed in a previous study that the combination of CTX + CCNU gave a better response rate than CTX alone. Their new study is using this regimen as a control and comparing it to CCNU + CTX + PCZ. At progression the crossover is to either ADM alone or ADM + VCR.

The Southwest Oncology Group has a Phase III study for disseminated squamous cancer in which a 5-drug regimen ("BACON" – BM, ADM, CCNU, VCR, HN_2) is compared to a 3-drug regimen called "NAC" (HN_2, ADM, CCNU).

The only lung cancer study of the Acute Leukemia Group B involves small cell carcinoma. Originally the study compared two courses of CTX + VCR + MTX vs. two courses of CTX alone, followed by 3200 rads to the primary tumor in 12 days with a subrandomization to half receiving an additional 3200 rads to the whole brain in 12 days. The induction chemotherapy was continued for four courses and patients in remission were then randomized to continued chemotherapy or no further treatment. This study was recently changed so that high-dose MTX + leucovorin is now used in the 3-drug regimen and standard MTX is included in the CTX alone arm.

The Radiation Therapy Oncology Group has been conducting studies to determine optimal definitive radiation therapy in inoperable lung cancer. Protocol 73-01 was designed for anatomic stage (clinical or surgical) T-3 and/or N-2 patients having non-disseminated disease and a histologic type of either squamous cell, adenocarcinoma, or undifferentiated large cell. The aim of the study is to define dose-response curves of local tumor and nodal control vs. complications in normal pulmonary tissues, and to determine the most efficient radiation therapy for improving the quantity and quality of survival.

Protocol 73-02 was designed for patients with a more advanced anatomic stage (T-4 and/or N-3), having non-disseminated disease and a histologic type of either squamous cell, adenocarcinoma, or undifferentiated large cell. The study is intended to determine the most efficient radiation fractionation schedule to achieve symptomatic and objective responses and to evaluate the effect of cytoxan subsequent to irradiation on the symptom-free and relapse-free interval.

Studies by the Southeastern Oncology Group are limited exclusively to disseminated small cell carcinoma of the lung. Their Protocol 357 is a Phase II

study comparing the effect of CTX alone vs. a combination of CTX + ADM + DTIC. Responders are randomized to one of the induction regimens with or without VCR, HU, and MTX (phase-specific therapy).

The Central Oncology Group studies are restricted to disseminated disease of all cell types. They have just completed a study comparing HXM vs. dibromodulcitol, in which HXM was felt to be superior, and have started a study comparing HXM and CTX. Pilot studies involve evaluations of ADM + CCNU and ADM + CCNU + HXM. In addition, their broad "solid tumor" Phase II studies of Yoshi-864 and 5-azacytidine have some input of lung cancer patients.

The Western Cancer Study Group has a protocol for inoperable epidermoid disease which compares 4000 R split-course radiotherapy + prednisone to the same therapy + BM. For all inoperable cell types there is a protocol examining 4000 R in 4-5 weeks plus the English drug ICRF-159. Another study for inoperable disease is investigating 4800R in 7-8 weeks plus coumadin (P.T. 30-40%).

The USC Cancer Center has a series of protocols for disseminated lung cancer. In adenocarcinoma of the lung they are attempting to determine the response rate to 5-fluorouracil and in other cell types they are evaluating the efficacy of bleomycin in previously unirradiated patients. Their major study for all cell types, except oat cell, is a randomized comparison of CCNU + HN_2.

Higgins summarized his report:

Since its inception in 1957, the VA Surgical Adjuvant Group has entered 9,114 patients with carcinoma of the lung, stomach, colon or pancreas, in 30 different protocols. In addition, an extensive pilot study on intra-arterial infusion was carried out by members of the group. Follow-up of the patients entered in the VA-Armed Forces study on asymptomatic solitary pulmonary nodules was taken over by the group and final analysis of the 392 cases of bronchogenic carcinoma has been completed. Protocols on carcinoma of the esophagus and head and neck cancer are in the stage of final completion. In addition, an immunotherapy arm is being prepared for the study on carcinoma of the large bowel.

One of the problems in conducting adjuvant trials has been the necessity of long follow-up when using survival as the study end point. Data are collected on first appearance of recurrent disease both clinically and histologically but inquiry into the possibility of using this as the end point has shown that little if any time could be gained. Early in the trial, sequential analysis was used in an effort to make an early determination of possible therapeutic benefit as well as to detect early harmful effects. The statistical office has again instituted a study of the possible use of sequential analysis in order to shorten the time that each protocol requires.

The original group was comprised of 21 hospitals and now consists of 29 members. Input of the individual participating hospitals as well as quality of data submitted is checked frequently. All material submitted is checked by the site chairman as well as the statistical office and this is periodically reviewed by the executive committee of the study group. Two participating hospitals have been dropped and an additional two are on probation at this time.

In lung cancer a total of eight trials has been conducted using chemotherapy or preoperative radiotherapy. Although the protocols were designed to answer a relatively simple question, extensive data have been collected and analysis of this material has been of significance in determining the natural history of lung cancer and other ancillary information. One of the most important contributions has been the demonstration that routine preoperative radiotherapy for lung cancer is contraindicated.

Approximately 250 patients have been entered in the current study using a combination of CCNU and Hydroxyurea. Additional information being collected in this trial concerns the value of big ACTH determinations in tissue and serum as a biologic marker in lung cancer. In addition, all clinical data is being evaluated in conjunction with findings at operation to study the TNM staging system for lung cancer. All histologic slides are being reviewed by a referee pathologist and information correlated with the diagnosis submitted by the hospital pathologist.

Close correlation with other lung cancer study groups, particularly the VA Lung Group and the Working Party for Lung Cc ncer is maintained. These and other groups studying more advanced disease have unfortunately not developed any regimen of great promise. After initial enthusiasm most of the surgical adjuvant studies in this country were dropped and VASAG has been somewhat alone in these endeavors in lung cancer.

The most promising approach appears to be multiple drug therapy possibly combined with immunotherapy. In the immediate future the group plans to institute combination immunotherapy-chemotherapy studies in head and neck and large bowel cancer. Preliminary discussion of a similar study for lung cancer has been instituted.

CONTRACT AWARDS

Title: Synthesis of potential anticancer agents
Contractor: Southern Research Institute, $638,688.

Title: Resynthesis of drugs and chemicals
Contractor: Monsanto Research Corp., $49,941.

Title: Synthesis of radioactive labelled compounds
Contractor: Stanford Research Institute, $209,990.

Title: New antineoplastic drug acquisition, evaluation, development & screening
Contractor: Parke, Davis, $99,178.

Title: Continuation of the development of a staging system for multiple myeloma patients
Contractor: Univ. of Arizona, $34,310.

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-CB-63981-37

Title: *Microcirculation and molecular transport in mammary carcinomas*
Deadline: *Sept. 4*

The studies formulated should be aimed at increasing our understanding of circulation within solid tumors. The primary objective is to elucidate conditions regulating transport of molecules from vascular into the cellular compartments of solid mammary tumors of human and/or animal origin.

Any approach to the problem is of interest provided it may have some relevance to the human tumors. Cell populations derived from human mammary carcinomas maintained in vitro and transplantable in nude-athymic mice are available for participants in the program of the Breast Cancer Task Force.

RFP NCI-CB-63986-37

Title: *Differentiation of mammary epithelial cells*
Deadline: *Sept. 4*

The studies formulated should be directed toward the differentiation of mammary epithelial cells as it relates to possible influences of other types of cells within the mammary gland. A major objective is to determine whether any of the several hormones involved in the epithelial differentiation exert their effect via another cell type within the mammary fat pad.

Additional kinds of dependencies of epithelial differentiation involving cell to cell interaction will be of interest provided they are based on some evidence which justifies an in-depth investigation.

Cell populations derived from human mammary carcinomas, maintained in vitro and transplantable in nude-athymic mice are available for participants in the Breast Cancer Task Force Program.

RFP NCI-CB-63985-37

Title: *Structure-function relationship of prolac[illegible] interactions in the mammary gland cells*
Deadline: *Sept. 4*

The studies should be directed at establishing: (a) which portion of the prolactin molecule is involved in binding to cell surface sites; and, (b) whether the same portion is responsible for hormone action(s).

RFP NCI-CB-63984-37

Title: *Glycoproteins of the mammary cell surface*
Deadline: *Sept. 4*

The project should be concerned with the turnover of glycoproteins from the malignant mammary cell surface and their release into the serum and/or mammary fluids. A characterization of released glycoproteins must be a part of the proposal.

Any approach is of interest, particularly the use of models relevant to the human disease. Cell populations derived from human mammary carcinomas, maintained in vitro and transplantable in nude-athymic mice are available for participants successfully funded for this project.

RFP NCI-CB-63983-37

Title: *Identification of mammary tissue*
Deadline: *Sept. 4*

The studies formulated should utilize immunologic or any other techniques for the identification, characterization, and quantitation of cell types present in mammary tissue at various stages of differentiation, including the examination of neoplastic tissues.

Cell populations derived from human mammary carcinomas, maintained in vitro and transplantable into nude-athymic mice are available for participatns in the Breast Cancer Task Force program of NCI.

RFP NCI-CB-63980-37

Title: *Osteotropism of mammary carcinoma metastasis*
Deadline: *Sept. 4*

The studies formulated should include conditions which determine: (a) localization of mammary neoplastic cells into bone tissue, (b) onset of osteolytic metastases and (c) hypercalcemia. Any approach would be of interest, particuarly the use of models relevant to the human problem.

Cell populations derived from human mammary carcinomas, maintained in vitro and transplantable in nude athymic mice are available for the participants in the Breast Cancer Task Force Program.

Contracting Officer for above 6 RFPs:
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