THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 4 No. 15
April 14, 1978

P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

Subscription $100 per year

ROGERS REAFFIRMS CONGRESS' INTEREST IN CANCER PROGRAM; ACT RENEWAL TO "BROADEN, SUSTAIN IT"

"The thrust of the legislation (renewing the National Cancer Act) is to continue the fight against cancer, to sustain it, to broaden it, and not to retreat," Congressman Paul Rogers, chairman of the House Health Subcommittee, told members of the American Assn. for Cancer Research last week.

Rogers said the bill which was scheduled to be marked up by his subcommittee this week would:

* Authorize distribution of reference chemicals and other test materials free to grantees, as well as contractors and other government

(Continued to page 2)

In Brief

NEW DCCP DIRECTOR TO BE NAMED SOON; CREECH, OWENS HEAD AACR, ASCO; CARBONE, MOERTEL NEXT

NEW DIRECTOR of NCI's Div. of Cancer Cause & Prevention will be named within a week, Arthur Upton told *The Cancer Letter.* NCI has been looking for a permanent director of the division since last September. . . . **NEW OFFICERS** of the American Assn. for Cancer Research and the American Society of Clinical Oncology: Hugh Creech, long time secretary-treasurer of AACR, is the 1978-79 president. Paul Carbone was elected vice president and president-elect last week. Albert Owens is the 1978-79 ASCO president, and Charles Moertel is the vice president and president-elect. Brigid Leventhal of ASCO and Fred Philips of AACR were reelected secretary-treasurer. . . . **AACR MEMBERS** voted down an effort to move the 1979 meeting from New Orleans because Louisiana has not ratified the Equal Rights Amendment. They refused to go along with the suggestion that selection of future meeting sites (after San Diego in 1980 and Washington D.C. in 1981—California has ratified ERA and D.C. has no voice in it) consider the issue. . . . **COMPREHENSIVE CENTER** evaluation, as reported by National Cancer Advisory Board site visit teams, will be the topic of the meeting of the NCAB Subcommittee on Centers May 16. The meeting is open. . . . **CLEARINGHOUSE SUBGROUP** on Experimental Design meeting scheduled for April 28 has been canceled. A plenary session of the full Clearinghouse is scheduled for May 15. . . . **CANCER CONTROL** & Rehabilitation Advisory Committee will meet May 2-3 at NIH Bldg 31 Room 10. . . . **BARBARA SANFORD**, due to become chief of the Biology Branch in the reorganized Div. of Cancer Biology & Diagnosis at NCI, will leave July 1 to become director of Research, Administration & Planning at Sidney Farber Cancer Center. . . . **NATHANIEL BERLIN**, head of the Breast Cancer Task Force (and of DCB&D) before leaving NCI for Northwestern Univ.: "The time has come to move the fundamental research portion of task force contracts to grants."

RFP Numbers To Drop Noticeably Soon, Upton Tells AACR . . . Page 2

Major Changes Being Considered By NCI For FCRC . . . Page 4

Abstracts Of Papers From ASCO Meeting . . . Page 5

RFPs Available . . . Page 7

Contract Awards . . . Page 6

PREDOCTORAL AWARDS, TEST MATERIALS FOR GRANTEES IN CANCER ACT RENEWAL

(Continued from page 1)

agencies (grantees may now receive biological materials but not chemicals).

* Authorize more than $1 billion for NCI in 1979 fiscal year.

* Emphasize Congress' interest in supporting predoctoral training awards.

* Earmark 50% of research service awards as institutional grants.

Rogers appeared determined to refute some of the Cancer Program critics and to reaffirm congressional support of the program.

"From the onset we have known this would be difficult, that answers might be long in coming, and that in the long run we might not be treated to a comprehensive solution," Rogers said. "This was not a 10-year effort to put a man on the moon. In the House report on the National Cancer Act of 1971, the committee emphasized that we had no way of knowing when a solution would come. We did not give rise to expectations of instant results.

"But we felt that that should not preclude the effort to conquer the disease. The 1974 report on renewal of the Act said it again. And we will say it again when we write up the bill next week. The National Cancer Act is recognition of the difficulties, and that we must bring national resources to bear on this adversary," Rogers continued.

"It is time to commit ourselves to sustaining the national effort." Not, however, without some adjustments to the program, he said.

"We've got to do more in cancer prevention—identifying the problems, taking action, coordinating actions among the agencies. I was pleased to see that we are starting on one, the smoking problem, and Secretary Califano has found that it is not easy. The thrust of his effort is to educate young people not to smoke. That is very important, and it is an approach that cannot be successfully resisted. I think even the executives of the tobacco companies would join in that effort."

Improved screening efforts and early detection are vital, Rogers, said, "but basic to it all is research. The primary purpose of NCI and the Cancer Act is to encourage research. The greatest weapon against cancer is knowledge. Then applying that knowledge through cancer centers and a network tie in with community hospitals.

"We want a program that is balanced. We expect appropriate funding for basic research.

"The committee was disturbed by the lack of predoctoral training awards. That was something that happened during the Nixon years. We have not been able to overcome it, largely because of the hangovers in OMB. We need to encourage young people, early in their careers, to enter biomedical research. The report on the bill will give emphasis to predoctoral awards. I think it is essential.

"Everyone talks about NCI being out of kilter with the other NIH institutes. Perhaps it is. The way to correct that is to bring up the others a little.

"This year we will authorize over $1 billion for the fight against cancer. I am hopeful that the appropriations committees will follow our lead and appropriate all of those funds. Those of you who know members of the appropriations committees should let them know how important that money is. A 1% increase (which the Administration asked for NCI, a total of $876 million) is not enough. Some say it should be at least 7%. It ought to be close to the authorized level."

AACR members, who interrupted Rogers several times with applause, cheered when he said, "Not only will you find the answers to cancer through your basic research in cancer, but you will also find solutions to other health problems."

Rogers said other changes in the Cancer Act would include authorizing cancer centers to engage in prevention research (which most of them do now anyway), and certain other minor amendments.

Rogers referred to a statement by Food & Drug Administration Commissioner Donald Kennedy, in which Kennedy compared the public perception of the Cancer Program with the Viet Nam war.

"This is not like Viet Nam," Rogers said. "This is a war which the American people support and Congress supports as well."

RFPs TO START NOTICEABLE DROP IN NEAR FUTURE AS REORGANIZATION TAKES HOLD

NCI's current reorganization will require several years to complete (in phasing out most research contracts in favor of grants), but "in the very near future there will be a noticeable dimunition in the number of RFPs going out on the streets," Director Arthur Upton told AACR members.

Upton restated the position he has made several times since initiating the reorganization, that "we will not seek to do anything disruptive." After eight months on the job, during which time he has taken a hard look at NCI's contract supported research, "it is not my view that we have much low quality research that can be sluffed off."

He assured grantees "who enjoy good relationships with our grant administrators, in most instances those administrators will be the same people."

Upton was enthusiastic about the Cancer Program.

"Never before in history has the field of cancer research been more productive or more promising," he said. "We are closer than ever before to understanding the genetic determinants and environmental factors in causing cancer. We estimate that 80-90% of cancers are linked to environmental causes and are, at least in theory, preventable. There is increasing pressure on NCI to look more carefully at these en-

vironmental factors.

"There have been marvelous advances in cancer treatment, particularly in the leukemias and lymphomas. We have the capability of putting into long term remission 90% of all but the most advanced cases of Hodgkin's disease, and in many instances, cures. With adjuvant chemotherapy, treatment of the more common tumors is highly promising.

"There is a revolution in attitudes, and with it, revolution in expectations," Upton continued. The National Cancer Program "gave impetus to these developments, enlisted the ablest minds, organized the resources, set up the machinery, and achieved admirable momentum. Despite these, evidence is growing that the public is skeptical, that there is disillusion and disenchantment."

NCI has had essentially a flat budget since 1975, and the 1% increase proposed by the Administration for 1979 would be used entirely for mandatory salary increases, Upton pointed out. This means "we will need to set priorities, and assure that resources will be devoted to activities with the greatest scientific merit."

Upton acknowledged that there is "increasing concern and clamor, in Congress and elsewhere, for us to change contracts to grants, as well as increase support for basic research. The first charge I had, (from President's Cancer Panel Chairman Benno Schmidt) was to look critically at this."

That critical look led to the reorganization, which will separate those with responsibility for program direction and administration from those responsible for peer review. It also will provide the opportunity "for investigators with grant applications to compete against all of the extramural funding pool, and open up the budgets of all the divisions to grantees."

Harold Amos, Harvard scientist who has been a member of the National Cancer Advisory Board since it was established by the National Cancer Act of 1971, said, "Much of the criticism of the Cancer Program is merely the advocacy of special groups.

"I'm speaking as an individual and not as a spokesman for the Board." He agreed there is a need "for a continued balanced attack."

Considering the role of chemical, physical, and biological agents, "you could say that 100% of all cancers have an environmental component," Amos said. "That says everything and it says nothing. Some say that if 70-80% of cancer has environmental origins, then 70-80% of the NCI effort should be in environmental carcinogenesis.

"Should we by next week be able to identify every carcinogen and remove them all, for most Americans over the age of 10, with some tumors, the environment already has settled in. Treatment remains the only hope for millions who will eventually get the disease even if all carcinogenic agents were to be removed immediately.

"It is important that NCI not be pressured into activities better left to the Environmental Protection Agency. NCI should get on with the vast program of identifying the causes and controlling malignant neoplasms," Amos concluded.

Albert Owens, director of the Johns Hopkins Oncology Center, discussed some of the problems facing cancer centers:

—Obligations placed on them by NCI and Congress without the funding required to fulfill those obligations.

—Lack of clear national program priorities.

—Instability of national program guidelines.

—Time consumed in review.

—Chronic partial funding.

"I was very pleased to hear Mr. Rogers say help is on the way in funding training," Owens said.

Partial funding is the most troublesome problem, Owens said. "The study section reviews us, assigns us a priority score and a carefully thought out budget, then because of NCI budget restrictions, we are funded at 80%. We are just now in our core grant at the level recommended in 1974.

"Why all the fuss about centers?" Owens asked. "Consider what have been the major advances in clinical oncology over the last 25 years. What type of institutions were where these advances were made? What were the resources required?"

Seymour Cohen, State Univ. of New York (Stony Brook), discussing cancer funding from the view of a lab scientist, based his presentation on the book, *Cancer Crusade: The Story of the National Cancer Act of 1971,* **by Richard Rettig (reviewed in the March 3 issue of *The Cancer Letter.*)**

Cohen noted that the book reported the opportunities for progress against cancer which formed the rationale for a massive increase in spending. Those opportunities, in 1971, seemed to be in virology, immunology, and chemotherapy, Cohen said.

"How have we done?" Cohen asked. "We do know the Virology Program has been successful, but essentially negative. The Immunology Program is still ongoing. There have been important acquisitions of knowledge in chemotherapy. But, did the existence of the Act contribute to those advances?"

Cohen referred to recent criticism of the Cancer Program in the *New York Times* which said the program is ailing, is the victim of inept administration, and that the time has come for systematic review of the progress made since the Act was passed.

"If these charges are not true, we should stand up and challenge them," Cohen said. "The leading figures on the Panel of Consultants (whose recommendations led to the Act) were leading figures in AACR, although they spoke as individuals. Our board has not spoken up, except in 1973. There is a struggle over the issue, is AACR a scientific organi-

zation exclusively, or should be become involved in political affairs that concern us?

"We can't afford not to become involved," Cohen concluded.

NCI REVIEWING FCRC OPERATION; MAJOR CHANGES THERE ARE BEING CONSIDERED

Major changes in NCI's operation of the Frederick Cancer Research Center are being considered, partly related to the current reorganization of the Institute, partly the result of the visibility of the $30 million a year program which is drawing fire from Congress and critics in the scientific community.

The House Appropriations Committee is conducting an investigation at FCRC and is almost certain to come up with some recommendations for changes.

The most significant changes, however—if any are made—probably will result from the reorganization thrust which is aimed at eventually moving support of most research, particularly basic research, from contracts to grants.

After NCI took over the former Army biological warfare facility in 1972, the National Cancer Advisory Board mandated that a basic research component be added to the other operations being developed. Michael Hanna was brought in to run that component, with a budget of about $5 million a year. Hanna's group has received high marks in reviews, but—it is supported entirely under the overall contract NCI has with Litton Bionetics.

FCRC is used primarily as a resource by NCI. It is a major supplier of test materials—viruses, chemicals, experimental drugs, and animals—for NCI's intramural labs and for many grantees and contractors.

A small but enthusiastically acclaimed visiting scientist program also is conducted there.

NCI Director Arthur Upton told the President's Cancer Panel this week that John Moloney, former director of the Viral Oncology Program, is heading an effort to develop a long range plan for FCRC. Upton pointed out that the Boards of Scientific Counselors of the Div. of Cancer Treatment and Div. of Cancer Biology & Diagnosis have reviewed different elements of the FCRC program. He also said the new Board of Scientific Counselors for the Div. of Cancer Cause & Prevention would also review parts of it. "We need a systematic way to bring those disparate reviews together, and focus them," Upton said. "The commitment is large, and we must assure ourselves that we are using those dollars effectively."

FCRC facilities are excellent, and the labs are considered superior to those on the NIH campus. The fact remains that the resources could be produced elsewhere, and the science could be done elsewhere, and the basis for a large portion of the criticism NCI gets would be removed.

"The original intention in taking it over was to make use of Frederick's unique facilities," Moloney told *The Cancer Letter*. "What we're trying to determine now is how to make optimal use of it."

Litton Bionetics, which operated FCRC from 1972-1977 under contract with NCI, was awarded a new five-year contract last year, The government has the right, however, to renegotiate the contract at any time, and even to phase it out, in less than five years.

Other items discussed at the meeting:

Earl Browning, chief of the Financial Management Branch, said staff was preparing the preliminary fiscal year 1980 budget for presentation to NCAB in May. It will be at two levels—$1.055 billion, and $1.153 billion.

The Senate HEW Appropriations Subcommittee has concluded its hearings on the FY 1979 bill, and is awaiting action by the House. The House HEW Appropriations Subcommittee has finished interviewing government witnesses, and will wrap up outside witnesses by April 21. Its markup of the bill is scheduled for the first week in May. Browning guessed that Congress will have the bill ready for the President in August or September. The fiscal year starts Oct. 1.

Browning said that NIH is preparing its 1980 budget presentation in a different format this year. The Office of Management & Budget finally has admitted that it is not competent to make budget decisions on a program basis, which NIH has provided in the past. This year, NIH will group its budget requests in four categories—science, clinical applications, technology transfer and training.

Upton told the Panel that NIH Director Donald Fredrickson had appointed William Raub, associate director for extramural and collaborative programs in the National Eye Institute, as NIH associate director for extramural research and training. That position has been vacant since Thomas Malone was moved up to deputy NIH director.

NCI executive officer Calvin Baldwin said that was "one of the half dozen top jobs at NIH." He predicted that Raub's job and that of Leon Jacobs, associate director for collaborative research, would be combined, which would place responsibility for establishing overall policy over 85% of NIH extramural funds in one position. This was recommended by Jacobs, but it probably will not happen until he retires.

Upton said that the Institute of Medicine, of the National Academy of Sciences, was considering making a full scale review of various aspects of the Cancer Program.

Benno Schmidt (who is still Panel chairman and will be until he is replaced, although his term expired last month), said, "I would welcome an outside sophisticated viewpoint on how they perceive the cancer control dollars could best be spent."

The Institute of Medicine did review the original Cancer Plan in 1972. It was suggested then that a followup review on the plan's implementation might

be in order. Panel member Paul Marks, who was on that review committee, agreed that it would be "extremely useful."

Schmidt wasn't sure. Speaking of scientists in general, he said, "It is clear that you can't keep your scientific respect and indicate anything but disdain for planning."

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 appeared last week in ***The Cancer Letter***, and the rest will be in next week's issue.

CYCLIC ALTERNATING COMBINATION CHEMOTHERAPY OF SMALL CELL BRONCHOGENIC CARCINOMA (SCBC) – M.H. Cohen, D.C. Ihde, B.E. Fossieck Jr., P.A. Bunn, M.J. Mathews, S.E. Shackney, A.V. Johnston and J.D. Minna, NCI–VA Medical Oncology Branch, VA Hospital, Washington, D.C.

High dose remission induction chemotherapy followed by alternating cycles of 2 or 3 non-cross resistant drug combinations was evaluated in 61 SCBC patients; 47 male, 14 female; 42 extensive disease, 19 limited; 32 performance status (PS) 1,17 PS 2; 12 PS 3.

Initially cyclophosphamide 1500 mg/M^2 d 1 and 1000 mg/M^2 d 21, CCNU 100 mg/M^2 d 1 and methotrexate 15 mg/M^2 twice weekly for 5 weeks (CMC) were given without dose modification for hematologic toxicity. Treatment was on the hospital ward. Prophylactic non-absorbable gastrointestinal antibiotics were intially used but were found to be unnecessary. Thirty-one patients received thymosin twice weekly for the first 6 weeks of therapy. On days 42 and 63 treatment consisted of adriamycin 60 mg/M^2, vincristine 2 mg and procarbazine 100 mg/M^2 daily for 10 days (VAP). On day 84 patients randomized to alternating CMC-VAP or to VP-16 125 mg/M^2 d 1,3,5 and ifosfamide 2400 mg/M^2 d 1,2,3 every 3 weeks for 2 doses (VP-IF). The latter patients received CMC-VAP-VPIF.

There were three infectious deaths during remission induction. After six weeks of treatment the complete response rate (CR) for limited disease was 42% and for extensive disease 24%. At 12 weeks 74% of limited and 40% of extensive disease patients had a CR. The overall response rate (CR+PR) was 95%. Addition of VP-IF did not increase the CR rate or survival. Patients with a CR at six weeks survived longer than patients entering CR at 12 weeks or later. Thymosin 60 mg/M^2 prolonged survival. The median survival for all complete responders is 14+ months. Two of the first 7 CR's in this study are disease free beyond two years.

Intensive chemotherapy with cyclic alternating drug regimens is highly effective in SCBC. Complete responders to treatment may have prolonged disease free survival.

SMALL CELL LUNG CANCER: A POTENTIALLY CURABLE NEOPLASM – Robert Oldham, Frank Greco, Ronald Richardson and Stephen Stroup, Vanderbilt Univ. Medical Center

We have treated 36 evaluable patients with small cell lung cancer with cytoxan, adriamycin and vincristine *CAV). Radiation therapy (3000 rads in 10 fractions) to the primary tumor and CAV were begun simultaneously. Cytoxan (1,000 mg/m^2), adriamycin (40 mg/m^2) and vincristine (1 mg/m^2) were given every three weeks for six cycles.

Toxicity was acceptable with this outpatient regimen. There were no toxic deaths and only 10 of 216 cycles required hospitalization for hematological toxicity. No cases of severe esophageal or CNS toxicity were seen. Consolidation chemotherapy with VP-16213 and hexamethylmelamine was well tolerated following CAV.

Of 36 patients, 16 had limited disease with 15 complete responses (CR) and 1 partial response (PR). With followup from 19 to 19 months, 75% of these patients are alive and disease-free. Of 20 patients with extensive disease, there were 11 CR's and 9 PR's. Thirty percent of these patients are still alive at up to 16 months. We have recently treated patients with extensive disease with high dose methotrexate plus CAV and have observed 7 of 7 patients achieving complete remission. Five of these patients are disease-free up to 6 months.

These data indicate that limited small cell carcinoma of lung is a highly treatable and potentially curable malignancy. Patients with extensive disease need trials with more aggressive combination chemotherapy.

NO INITIAL THERAPY IN THE MANAGEMENT OF ADVANCED (STAGES III, IV) NON-HODGKIN'S LYMPHOMAS WITH FAVORABLE HISTOLOGIES – Carol Portlock and Saul Rosenberg, Stanford Medical Center

Treatment of advanced lymphocytic lymphomas (nodular or diffuse)—NLPD, NML, DLWD—remains controversial because prognosis is good, even with single alkylating agent therapy (SA). Since 1962 at Stanford, the practice off protocol study has been to defer initial treatment if patients were relatively asymptomatic, without threatening disease. Forty-four previously untreated patients with stage III (6) or IV (38) disease have been followed (NLPD=21, NML=8, DLWD=7, DLPD=7) from 3-133 months, median=37 months. Twenty-five patients have required treatment, usually for bulky lymphadenopathy, 13 with SA, six with combination chemotherapy, and six with palliative irradiation. Median time to treatment was 31 months for all patients with the median for NML (nine months) significantly shorter than for NLPD (38 months) (p=.02) orDLWD (8+ years) (p=.008).

There have been seven deaths: none in the NLPD or DLWD groups, 4/8 in NML and 3/7 in DLPD. The actuarial survival for all patients is 68.4% at 10 years, with no significant differences noted among histologic subgroups (median survival: NLPD=10+ years, NML=44 months, DLWD=8+years, DLPD=59 months) (p greater than .07) Though this is a selected series, it will be documented that these patients are representative of common clinical presentations of these diseases.

Careful observation without initial therapy is an appropriate option in the management of patients with relatively asymptomatic advanced non-Hodgkin's lymphomas with favorable histologies.

CIS-PLATINUM (DDP) FOR COMBINATION CHEMOTHERAPY OF OVARIAN CARCINOMA: IMPROVED RESPONSE RATES AND SURVIVAL – H.W. Bruckner, R.C. Wallach, B. Kabakow, E.M. Greenspan, S.B. Gusberg, J.F. Holland, Mount Sinai School of Medicine

Patients with advanced ovarian cancer are currently treated with DDP 50 mg/M^2, Q3W, in combination with adriamycin (ADM) 50 mg/M^2, Q3W or thio-TEPA 10 mg/M^2, D1,2 Q3W, or a new regimen consisting of DDP-ADM plus cyclophosphamide (CYC) 150 mg/M^2, D2-8 and hexamethylmelamine 150 mg/M^2, D2-8 (CHAP), as part of two controlled initial chemotherapy trials. Patients failing prior chemotherapy are currently treated with DDP-ADM, 30 mg/M^2, plus CYC, 300 mg/M^2(CAP) or high-dose DDP, 120 mg/M^2 bolus VS 4-hour infusion in a controlled trial. As initial therapy DDP-ADM produced 11/30 complete responses, 13/30 partial responses, and only 6/43 failures (progression within six months), compared to DDP-thio-TEPA: 5/19, 7/19, and 5/26. Early CHAP response results for 15 patients are similar to date. Survival at 18 months with DDP-ADM is 10/14 (two with disease) and 24 months is 7/10 (two with disease).

DDP-thio-TEPA survival is similar to DDP-ADM for the first 12 months. The DDP-thio-TEPA arm has been discontinued because of more episodes of severe leukopenia and thrombocytopenia of long duration compared to DDP-ADM. Response rates after failure of a standard alkylating agent were DDP-ADM 7/15, and CAP 10/15. 5/10 patients treated with high-dose DDP responded. Instances of paresthesia have been observed. Thus: DDP produced at least an additive effect. DDP may increase the frequency and severity of anemia, leukopenia, and thrombocytopenia in combination therapy; nevertheless, it can be added to some cytotoxic regimens, particularly for the induction phase of treatment.

DDP improved survival and chance of complete remission of patients with advanced ovarian cancer.

RANDOMIZED TRIAL OF ADJUVANT THERAPY FOR 'HIGH RISK' PRIMARY MALIGNANT MELANOMA – Sheldon Kaufman, Robert Carey, A. Benedict Cosimi, and William Wood, Massachusetts General Hospital, Harvard Medical School

Retrospective pathologic classification of 213 patients with malignant melanoma has clearly identified a group at high risk of recurrence after resection for apparent cure. These patients have deeply invasive tumors (Clark's Level III, IV, V, with vertical thickness greater than 1.5 mm) and/or metastasis to electively removed regional lymph nodes. The observed recurrence rate in these patients was 25% at 12 months and 50% by 5 years. 'High risk' patients have been assigned to one of three forms of adjuvant therapy (DTIC vs BCG vs DTIC + BCG) immediately after definitive surgery and continuing for 24 months. Sixty-three patients have been followed from 2-24 months (average 12). These groups are comparable by level, nodal status, age, sex and primary site.

In the DTIC group, recurrence has been observed in 5/19 patients and four patients have died. In the BCG group, there have been 4/24 recurrences with two deaths. In the combined therapy group, there have been no recurrences or deaths in 20 patients. Statistical evaluation reveals no difference in recurrence or death rate between the DTIC-treated and BCG-treated patients or between these groups and the previously untreated patients. Combined therapy patients, however, appear to have a decreased rate of recurrence (p less than 0.05) and improved survival (p less than 0.05). These data strongly support a beneficial effect of combined chemo-immuno adjuvant therapy for patients with high risk malignant melanoma. Further patient accrual and followup is continuing.

LONG TERM RESULTS OF COMBINED MODALITY THERAPY FOR ADVANCED HODGKIN'S DISEASE – Leonard Farber, Leonard Prosnitz, Joseph Bertino, Ed Cadman, David Fischer, Richard Lutes, John Pezzimenti, Yale Univ. School of Medicine and Yale-New Haven Hospital

In 1969 we introduced a new treatment program for advanced Hodgkin's disease (PS IIIB and IV and patients who relapsed following curative radiotherapy) employing 5-drug combination chemotherapy and low dose radiotherapy to all pretreatment areas of involvement with disease. The drugs used were HN2, VCR, VLB, procarbazine and prednisone—the radiation dose was limited to 1500-2500 rads.

This report updates some of our previously published results. One hundred thirty-five patients have now been treated and followed a minimum of one year. The previously reported results have not changed significantly with the passage of time. The complete remission rate remains at 75%. The cumulative relapse rate is 11% at five years. Of the original 80 patients analyzed in 1975, 60 had achieved complete remission with five of those 60 subsequently relapsing. With the mean followup now in excess of five years, an additional four patients have relapsed for a total of 9 of 60 or 15%. This relapse rate remains significantly less than the best reported relapse rates with chemotherapy alone which range from 35-50%.

Assuming complete remission rates of 75% and subsequent relapse in 10-15%, combined modality therapy is potentially curative for two-thirds of patients with advanced Hodgkin's disease.

ABSENT ESTROGEN RECEPTOR AND DECREASED SURVIVAL IN HUMAN BREAST CANCER – W.A. Knight III, R.B. Livingston, E.J. Gregory, A.I. Walder, W.L. McGuire, Audie Murphy VA Hospital and Univ. of Texas Health Science Center

We previously reported, in a series of 145 patients undergoing mastectomy for primary breast cancer, that those with negative estrogen receptor determinations have increased risk of recurrence. The proportion of patients who were estrogen receptor negative was similar regardless of the pathological stage (I or II); the type of mastectomy; modified vs. radical; the use of post-operative radiotherapy; the location of the primary within the breast; or the size of the primary. However, more premenopausal patients were estrogen receptor negative, 48% vs. 32% (p. less than .05). Recurrences are now documented in 20 estrogen receptor- and 14 estrogen receptor+ patients (37% vs. 15%, p less than .01) with a median followup of 20 months in both groups.

Thus far, 11/54 estrogen receptor- and 5/91 estrogen receptor+ patients have died of breast cancer (20% vs. 6%, p. less than .01). Of patients with axillary node involvement, 10/29 estrogen receptor- and 5/54 estrogen receptor+ patients are dead of breast cancer (35% vs. 11%, p. less than .05). Although the death rate was the same in premenopausal (6/48) and postmenopausal (10/97) women (13% vs. 10%), estrogen receptor status was a prognostic factor for survival within each group: 5/23 estrogen receptor- and 1/25 estrogen receptor+ premenopausal have died (22% vs. 4%) and 7/31 estrogen receptor- and 3/66 estrogen receptor+ postmenopausal patients (23% vs. 5%) have died of breast cancer.

We conclude that absence of estrogen receptor in a primary breast specimen is a major prognostic indicator for early recurrence and worse survival in women undergoing mastectomy.

ADVANCED OVARIAN ADENOCARCINOMA: MELPHALAN (PAM) VS. COMBINATION CHEMOTHERAPY (Hexa-CAF) – Robert Young, Bruce Chabner, Susan Hubbard, Richard Fisher, Richard Bender, Tom Anderson, Vincent DeVita, NCI

Eighty patients (pts) with advanced (FIGO stage III & IV) untreated epithelial ovarian cancer were randomized to receive either PAM (0.2 mg/Kg p.o q.d.X5 q4-6 wks) or Hexa-CAF (5-FU 600 mg/M^2 and methotrexate 40 mg/M^2 I.V. on days 1 & 8, cyclophosphamide and hexamethylmelamine 150 mg p.o. daily for 14 days). 37/39 pts on PAM and 40/41 pts on hexa-CAF have been on study more than 6 mos and are evaluable for response. The two groups are similar in stage, age, histologic type, initial surgery and residual disease. Approximately 80% of each group had residual disease greater than 2 cm after surgery.

After completion of therapy pts were restaged with peritoneoscopy and/or laparotomy. For pts receiving PAM, complete remission rate (CR) is 6/37 (16%), partial remission (PR) 14/37 (38%) and no response (NR) 17/37 (46%). For pts receiving hexa-CAF, CR 13/40 (33%), PR 17/40 (43%), and NR 10/40 (25%). Overall response rate with hexa-CAF is statistically better (p. less than .05) than with PAM. The difference between 33% CR with hexa-CAF and 16% CR with PAM is at p=.08). Overall median duration of survival for hexa-CAF is 29 mos vs 17 mos for PAM. Regardless of therapy pts achieving documented CR have long survival, median will exceed 36 mos, 15/19 CRs still surviving. Pts with minimal residual disease have a higher overall response rate 16/19 (84%) vs 31/58 (53%) for those with residual disease greater than 2 cm (p. less than .05).

Treatment of advanced ovarian cancer with hexa-CAF is associated with statistically higher overall response rate (76% vs. 54%). More CRs (33% vs 16%) and longer overall survival (29 mos vs 17 mos). This randomized trial demonstrates for the first time a combination chemotherapy regimen which is better than a single alkylating agent in advanced ovarian cancer.

CONTRACT AWARDS

Title: Implementation of the hospice concept for the care of terminal cancer patients
Contractor: Hillhaven Foundation, Tacoma, Wash., $1.7 million.

Title: Technical support for the ICRDB Program
JRB Associates, $1,350,632.

Title: Research program to acquire and analyze information on chemicals that impact on man and his environment
Contractor: Stanford Research Institute, $93,500.

Title: Synergistic interaction of hormones and neutron radiation for mammary gland carcinogenesis, supplemental
Contractor: Organization for Health Research, The Netherlands, $69,000.

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.

SOURCES SOUGHT

RFP NCI-CP-VO-81039-66

Title: *Operation of a facility to provide and maintain nonhuman primates for cancer research*

Deadline: *(For submission of resumes) Approximately April 28*

NCI is seeking organizations having the capabilities and experience to continue carrying out a project for the operation of a facility to breed and maintain a variety of species of nonhuman primates which will provide fetuses, neonatal and maturing animals for cancer research.

Interested organizations will be expected to have as a minimum: 1) Three continuous years of experience starting no later than 1974 in the operation of both an old and a new world nonhuman primate breeding program producing at least 50 young each year. 2) The facility must have a current AAALAC accreditation and the capability for housing approximately 100 individually caged old world breeders, the conventional caging of approximately 80 old world juveniles, cages and room space for breeding and holding approximately 130 marmosets and approximately 175 owl monkeys, and room space for the conventional caging of small groups of several other new world species. 3) Quarters for the conditioning and isolation of newly received animals from established resident animals with a system of cages and isolation rooms to prevent exchange of infectious organisms between species. 4) A nursery for the hand rearing of normal and experimental young in isolators maintained under negative pressure. 5) A biohazard containment area for housing approximately 400 old and new world monkeys ranging from post-nursery to adult age inoculated with potentially oncogenic materials. Change room and shower facilities as well as the capability for autoclaving all contaminated materials leaving this area would be required. 6) Maintain a breeding colony of at least 21 white handed gibbons consisting of 12 adults and nine juveniles. 7) Laboratory support services in hematology, bacteriology, virology, biochemistry, gross and histopathology, and chemical medicine for both the normal and inoculated animal.

The primate facility must be located within a 60 mile radius of NIH to facilitate rapid exchange of study materials such as live viruses, actively multiplying cell cultures, tissues, and to permit discussion, planning, and analysis of experiments with NIH scientist for whom the project is maintained. Any proposed moving of the project from the incumbent contractor's location must be accomplished rapidly with least possible disturbance to breeding and experimental animals. The description of capabilities to manage this project should describe the methods and means that would be used to move the animals from their present location in Kensington, Md. to the new facility.

Resumes of experience and capabilities should cover the names, professional qualifications, and experience of scientists and technical personnel available for the project and the availability and description of facilities required to perform the project.

Fifteen copies of the resume of experience and capability must be submitted to:

Contract Specialist: Clyde Williams
Viral Oncology
301-496-1781

RFP NO1-CP-85628-59

Title: *The use of physico-chemical parameters in obtaining structure activity relationships in potentially cancer related end points*

Deadline: *May 15*

NCI is interested in establishing a contract(s) for determining physico-chemical factors which influence the potential cancer related endpoints of compounds. Purpose is to gain insight into the mechanims of carcinogenesis, to develop capabilities which could be applied to predicting effects of untested compounds in living systems as well as to correlate bioassay results for risk assessment. This will involve correlating physico-chemical properties of molecules to then known activity using mathematical techniques, i.e., funding structure activity relationships (SAR).

A thirty-eight (38) month contract is anticipated.

Contract Specialist: Reginald Holloway
Carcinogenesis
301-427-7914

RFP NO1-CP-85618-69

Title: *Development and validation of standard procedures for the nutritional assessment and monitoring of adult and pediatric cancer patients and normal individuals*

Deadline: *June 14*

The primary objective of this project is to establish techniques for evaluating, in both field and clinical settings, the nutritional status of pediatric and

adult individuals, with and without cancer. This requires the following:

To identify potential techniques; to validate the techniques; to evaluate the acceptability of these techniques to both normal controls (the population at large) and to the cancer patient; to determine which techniques are applicable in both a field and clinical setting, taking into account the problems associated with certain tumor types and treatment modalities; to determine mean values and ranges in normal subjects as well as cancer patients; and to define in detail the procedures to be used.

Contract Specialist: Linda Waring
Carcinogenesis
301-427-7574

RFP NCI-CP-VO-81035-63

Title: *Immunoprevention of cancer in cats*
Deadline: *June 2*

NCI is seeking qualified organizations to conduct studies on the immune prevention of cancer in the cat. This project will attempt to define the feline transforming gene (src) and its protein product. In addition, the relationship between expression of the src gene and expression of FOCMA will be defined in naturally occurring and/or environmentally induced feline cancer; the feasibility of immunization with FOCMA and/or feline transforming protein for immune prevention of cancer in cats will be determined.

Specific experience in the following areas is required: (1) Purification of oncornavirus protein and cell surface antigens; (2) preparation of monospecific heterologous antisera to purified oncornavirus proteins and cell membrane components; (3) biological and biochemical characterization of expression of the transforming gene (src), isolation and characterization of its protein product; and (4) induction of immunity by purified antigens and/or antibodies.

Contract Specialist: Jack Labovitz
Viral Oncology
301-496-1781

SUBCONTRACT ANNOUNCEMENT 78-A-1

Title: *Long term carcinogenesis bioassay testing*
Deadline: *See below*

Carcinogenesis bioassay testing using mice and rats for the test of a variety of chemicals. Administration of the test agents may be by dosed-feed, dosed-water, gavage, or skin-painting. A highly qualified veterinary or medical pathologist with experience in laboratory animal rodent pathology, a veterinarian qualified in laboratory animal science, an HT/ASCP registered technician, a chemist, and a toxicologist must be available for the program.

Chemistry, histology, and pathologic diagnosis activities may be a subcontractual arrangement. Facilities for dosing and maintaining animals in a situation that will maintain the integrity of the experiment and will permit safe operations for animals and laboratory personnel are necessary. A basic ordering agreement (BOA) cost-plus-fixed-fee (CPFF) type of subcontract is contemplated.

Please indicate in your request letter how many chemicals you feel you are qualified to test at a time, i.e., 2,3,6,9, or more; the time frame for handling testing, e.g., "Cannot handle any tests now, expect to be able to handle three chemicals around Sept. 1978," and the route(s) of administration capabilities.

Interested laboratories should request Tracor Jitco's Bidder's Mailing List Application and BOA 78-B-1. Those companies currently on the program will be sent a copy of the BOA package automatically. There is no deadline for submission; laboratories will be analyzed for qualification on a quarterly basis. Technical proposal received by May 30, 1978 will be acted upon from June 1 through 15; by Aug. 31, from Sept. 1 through 15, etc. Announcements will appear periodically; this is Announcement 78-A-1. (093)

Tracor Jitco Inc.
Attn: Subcontract Administration
1776 E. Jefferson St., Rockville, Md. 20852
301-881-2305

RFP NIH-NINCDS-78-10

Title: *Laryngeal carcinoma: Identification of high risk factors*
Deadline: *June 23*

The research will be an integration of the presently available epidemiological information on the incidence of disease and death due to laryngeal carcinoma. The purpose is to identify those individual, health, environmental, and occupational factors which will delineate persons at high risk of laryngeal carcinoma in the U.S. today. The project will include an integration of information in the literature, and examination of mortality and incidence data, and a study of the independent and/or interactive relationships of various factors to the incidence of laryngeal carcinoma.

National Institutes of Health
National Institute of Neurological and Communicative Disorders & Stroke
CMB Federal Building, Room 1012
7550 Wisconsin Ave., Bethesda, Md. 20014
Attn: P. Davis

The Cancer Letter —*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090.