THE CANCER LETTER
RESEARCH EDUCATION CONTROL

Vol. 2 No. 49
Dec. 3, 1976

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Subscription $100 per year

FLOOD SAYS CONGRESS WILL RENEW CANCER ACT, BUT ONLY AFTER "ALL OUT" REVIEW OF RESEARCH POLICY

Daniel Flood (D.-Pa.), chairman of the House HEW Appropriations Subcommittee, has predicted that Congress will renew the National Cancer Act next year but only after "an all-out investigation of research policy beyond anything we've seen."

This intensive review will produce "some sort of rational system . . . of determining research priorities," Flood said. Application of research

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In Brief

CARTER TRANSITION TEAM LISTS PROSPECTS FOR HEW SECRETARY; INTERFERON AVAILABLE

NEW HEW Secretary could come from this list, drawn up by President-elect Carter's transition team: Reps. Barbara Jordan and John Brademas, former Rep. Patsy Mink, former Presidential assistant (to Lyndon Johnson) Joseph Califano, black leaders Marion Wright Edelman, Vernon Jordan, and Aileen Clarke Hernandez, Notre Dame Univ. President Theodore Hesburgh, welfare consultant Tom Joe; Grace Oliveras, staff member of the New Mexico governor; former HEW official William Page; Jule Sugarman, former New York and Atlanta city official; and Mitchell Sviridoff, Ford Foundation vice president. . . . **INTERFERON WORKING** Group will distribute interferon to qualified scientists requesting it. NCI is in the process of obtaining a supply of human leucocyte, human fibroblast (diploid) cell, and human lymphoblastoid cell interferons. The human leucocyte and fibroblast interferons are being prepared for use in clinical studies. Send requests to the working group, NCI, Room 3A03, Bldg 31, Bethesda, Md. 20014. . . . **CORRECTION**: James Luce, Mountain States Tumor Institute, was reported in the Nov. 5 issue of *The Cancer Letter* as joining the staff of the Northern California Cancer Program. Actually, Luce will be director of community and clinical activities for the West Coast Cancer Foundation, one of the component members of the consortium in the Northern California Cancer Program. . . . **GEORGE MILLER**, director of the Univ. of Illinois Center for Educational Development, will deliver the annual Harvey Lecture at the American Assn. for Cancer Education meeting Dec. 10-11 in Charleston, S.C. . . . **LEE CLARK**, president of the Univ. of Texas System Cancer Center, member of the President's Cancer Panel, and ACS president: "If I were to suggest a reorganization of NIH, which no one has asked me to do, I'd suggest that other institute directors have the same opportunity to present their budget to the White House that NCI has. . . . When NCI was set up as the first categorical institute in 1937, some said that it would destroy the National Health Labs, but within 10 years, that became the National Institutes of Health. Cancer has led the way in stimulating interest in categorical disease problems."

CONGRESS WILL INSIST ON APPLICATION OF RESEARCH RESULTS, FLOOD SAYS

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results will be the primary measurement of the success of the Cancer Program—"We'd better see some improvement in official morbidity and mortality figures by the next renewal," Flood warned.

Flood made his remarks at a symposium at Hershey Medical Center, and he left little doubt about what he expects from the Cancer Program.

Pointing out that, while he is not a member of the health authorizing committees which will process renewal of the Cancer Act, "I'm the guy that puts your money where his heart is." Flood said, "When all the authorizing is done, when all the shouting and statistics-flinging is finished, you still don't have a dime. Not a farthing. Not a sou.

"I've backed the Cancer Program to the hilt. I'll do it again. But I have a right to expect, and I think I'm in a position to demand, that you keep the patient foremost—not the lab, not the department, not the academic journal (all those are necessary)—but the patient foremost in mind.

"Where the clinical research statistics show higher survival rates, I want the physicians across Pennsylvania to know quickly how to achieve those rates among their own patients.

"I don't want a two or three year delay between the discovery that post operative chemotherapy is a must at Hershey Medical Center and the discovery by the family physician that it is a must. You basic researchers must help. You must advocate with the patient in mind. He's paying for your research grant."

Flood said that "you'll be under more intense scrutiny next year than ever before. Make sure that you do your homework—that your outreach programs don't bypass Wilkes-Barre, Scranton, Luzerne County. Get out of your ivory towers. Get the best possible treatment to the patient."

Application of research results no longer will be tolerated as a byproduct, Flood insisted. "There will need to be explicit administrative mechanisms to achieve results. Serendipity is a sine qua non of basic research. But we can no longer leave to serendipity the wending of a research product from the laboratory to the patient.

"That is why I am confident that the National Cancer Program, if properly defended and properly administered between now and then, can stay ahead of the game—with your cancer centers, with your disease control programs, with your commitment to targeted research—where targeted research is scientifically appropriate."

Flood said he expects the "rational system" for determining research priorities will include epidemiological guidelines "on what diseases are doing the most damage, which ones hit the most people, which ones cost the most. And I don't think cancer research will suffer by any of those crude measures. As a matter of fact, as I look at the epidemiological data that are available to us now, as sparse as they are, I don't think that Congress had done a bad job at all in making the Heart and Cancer institutes the biggest ones at NIH.

"I don't even think the politicians did badly in assigning those two institutes disease control studies. After all, what has been bringing the death rate down in the last couple of years? I'll tell you what. It is quite likely our investment in stroke programs that began with Regional Medical Programs. And it is quite likely the attention given to anti-hypertension programs, case finding, screening and chemotherapy for hypertension.

"Now Nobel Prizes (work alone) didn't achieve these life saving programs. The Nobel Prize work was there. But the mounting of these programs resulted from the advocacy of medical sophisticates who saw life saving opportunities in research products already available. The research, basic and applied, has been done. It took advocacy, though, to impact the death rates."

Flood noted that "many of us in Congress have put our political substance on the line for the Cancer Program. When the 1970 Panel of Consultants said that a couple of decades of basic science work had opened up several explicit new opportunities for rapid research exploitation, I believed them.

"When the Panel of Consultants in 1970 said that cancer is the most dreaded disease, I believed them. When the Panel said that enough basic work had been accomplished so that a step by step work program could be designed, I believed them. And when the Panel said that the way to get the word out to the medical profession was to establish a chain of specialized and comprehensive cancer centers, I believed them.

"Now it's your turn to believe me. I've been accused of joining the Disease of the Month Club. I've been challenged by professors from one end of this country to the other for my commitment to the National Cancer Program. I've been told that the 1970 Panel was all wrong, that NIH is perfect, that all we need to do is turn the investigators loose in the labs and all will be well. We sit back and wait. Along comes penicillin. Along comes antibiotics. Along comes polio vaccines. . . .

"I think that Congress had been through the mill on this one—so much so, in fact, that Congress is now going to have its say.

"Next year the House and Senate, I predict, will each have lengthy, intensive hearings on our national health research policy. I am not a member of the health legislation authorizing committees. But I am convinced that they are planning an all out investigation of research policy beyond anything we've seen.

"The original National Institute of Health, which was the National Cancer Institute, did not inspire the

amount of debate that will take place over research policy in the coming year. I was there. It was a blip on the health policy radar. What's coming is an electrical storm."

Flood was first elected to Congress in 1944. Republican landslides swept him out in 1946 and again in 1952, but he fought his way back after each defeat. He has been chairman of the HEW Appropriations Subcommittee since 1968.

AMES, YARMOLINSKY DESCRIBE IN VITRO SYSTEMS FOR CARCINOGENESIS TESTING

The prospect that quick and inexpensive tests to determine the carcinogenicity of chemicals could be devised to replace the slow and very expensive animal tests now being used has long intrigued scientists in the carcinogenesis field. NCI has for several years supported development of in vitro carcinogenesis tests, although not as enthusiastically as it should, some critics have charged.

Two of the more promising in vitro test systems were described by their principal proponents at the recent meeting of the National Cancer Advisory Board.

Bruce Ames, Univ. of California professor of biochemistry and a member of the Board, described his salmonella mutagenesis sytem, the best known and probably the most advanced of the in vitro tests.

Ames said he started working on a mutagenesis system when he was working at the National Institute of Arthritis, Metabolism & Digestive Diseases. "I had read too many labels on potato chip packages," he said.

Ames' test involves the application of a suspected carcinogen to salmonella bacteria, which are then observed for mutagenic changes. The test, after being refined to improve its sensitivity, is 90% accurate in predicting carcinogenicity, Ames said, and he feels that it can be improved to 95%.

"We're getting a very high percentage of known carcinogens that are working in the test," Ames said. "The theoretical reason is that the way these chemicals were working to cause cancer is that they are causing mutations, and here is an effective way of picking up mutagens.

"What about the 10% we're missing?" Ames continued. "Some I think we're never going to get because they are hormones or hormone analogs that are causing cancer through a non-mutagenic mechanism. One could ask, why aren't most chemicals that cause cancer acting as hormones rather than mutagens. I think the reason is that a hormone has to interact with a receptor and a very specific interaction, while to get a mutagen is relatively easy. . . .

"I think that perhaps one half of the 10% are mutagens and will show up in other systems. With a little more fiddling, in a year or two we'll be up to 95%, and I suspect that is the best we can hope for."

Ames said diethylstilbesterol is one known carcinogen that does not shown up positive in his test "because it is working through a non-mutagenic mechanism . . . in some way unique to animal cells."

Ames said his lab has looked at large numbers of chemicals that a re close relatives of known carcinogens but have been found in animal tests to be non-carcinogenic themselves. Many of them were found to be "a little bit mutagenic" which has convinced him that the salmonella test is considerably more sensitive than animal tests. "Most of the false positives in animal tests, we think, is just the insensitivity of animal tests," Ames said.

"The more general problem is how to calibrate these in vitro tests if in some ways they are more sensitive than animal cancer tests," Ames continued. "I don't think false positives are too important. The key thing is, how many are each test going to miss. If you have a number of tests, I think that would cover most of them."

The question of potency is a sticky one. "Even though you are getting 90%, what about potency?" Ames asked. "Is there any relationship between mutagenic potency and carcinogenic potency? How do you calculate carcinogenic potency? That is sure to get you into a big argument with the animal cancer people."

Ames said that tar in cigarette smoke is quite mutagenic, and for that reason some tobacco companies are using his test to find the mutagenic elements in the smoke, hoping that will help them devise filters to get those elements out of the smoke.

One advantage of his test over animal tests is that it can be used to look at a complex mixture of substances, he said. He suggested that it would be useful in studies of various diets to help determine why different population groups have widely differing cancer rates, "to fish out the mutagens" in foods.

Ames suggested that human exposure to mutagenic chemicals might be responsible for birth defects, heart disease and aging diseases.

Animal tests require two to three years and cost about $100,000 for each chemical. The Ames test takes only one to two days and costs less than $100.

Another system that can be completed in less than a day was described by Michael Yarmolinsky, director of carcinogenesis research at Frederick Cancer Research Center.

This test is called the prophage induction test, in which bacteria which harbor a latent virus, called a prophage, are exposed to a suspected carcinogen. An hour later the fluid is tested to see if the bacteria have released the virus which has been detected in plaque forming units. These plaques can then be assayed in a period of about six hours, Yarmolinsky said.

"If we ask what kind of substances in the environment affect the incidence of cancer, we can say that in many cases the evidence points to agents that have as their ultimate target DNA," Yarmolinsky said.

"For one thing, carcinogens are specifically active on tissues in which DNA synthesis is continuing. Epithelial tissues, for example, which continue to divide after other tissues have ceased to do so, are subject to the action of carcinogens. As you well know, cancer is predominantly a disease of the epithelial. Embryonic tissues are also sensitive to carcinogens, as are tumors themselves.

"In fact, many agents which inhibit uncontrolled tumor growth are themselves carcinogens. That means to me, that if we search the environment for carcinogens, not only are we likely to find them, we are likely to find as well some antitumor agents.

"More specifically, we can say that carcinogens are often agents that cause lesions in the DNA. These lesions block the synthesis of DNA at least temporarily, and they cause mutations."

Yarmolinsky acknowledged that the test would produce false positives and false negatives. "For example, we may expect reagents whose target is not DNA but elsewhere along the path to induction, might show as inducing agents but not be carcinogenic."

One possible advantage of the induction test over the mutagenic test would be that certain compounds which are toxic to bacteria would not allow them to form a clone, but would allow them to show phage induction.

Yarmolinsky said the research at Frederick will attempt to develop modifications of the induction test. "We hope we'll be able to come up with something that will be useful, if not as a general screen, then for certain specific purposes."

The Cancer Letter learned that NCI plans to use the Ames test in its Carcinogenesis Program, primarily to help in the selection process in determining which chemicals will be tested. It will be an addition to the factors which have been used in that determination, and some Ames negatives will be tested anyway. Also, compounds already in under test will be run through the Ames system. NCI plans to use the Ames test not only for prescreening but also as an aid in research to learn more about the mechanisms of carcinogenesis.

"The Ames test is a revelation, and a boon to our armamentarium and capability to do research on the biological events that are carcinogenesis and mutagenesis," an NCI executive said. "It is easy, cheap, and rapid."

However, no in vitro test is capable of measuring such items as absorption, distribution, and metabolism, "or things that happen as the compound enters the target cell. But the Ames test does measure the bottom line in molecular events."

NCI does not consider the prophage induction test as having any practical application at the present time. The feeling is that inhibition of DNA synthesis, if in fact that does play a role in carcinogenesis, could better be demonstrated in other systems.

REP. CARTER, TOP GOP HEALTH GROUP MEMBER, TO SPEAK AT ACCC MEETING

Congressman Tim Lee Carter (R.-Ky.), top ranking Republican on the House Health Subcommittee which will hold hearings next years on renewal of the National Cancer Act, will be the keynote speaker at the third annual conference of the Assn. of Community Cancer Centers.

The conference will be held Jan. 28-30 at the Key Bridge Marriott Hotel in Arlington, Va., just across the Potomac from Washington D.C.

Carter, who claims no blood relationship at all with the new President and probably very little kinship in political philosophy, will speak at the Saturday, Jan. 29, luncheon. A conservative, Carter has supported the National Cancer Program.

BREAST CANCER REPORTS DEMONSTRATE NEED FOR MORE RESEARCH, GULLINO SAYS

The "Report to the Profession" on breast cancer was a "rather informative meeting that did what it was supposed to do—present a panoramic view of the situation as it now exists," according to Pietro Gullino, chairman of the Breast Cancer Task Force.

The scientists who reported on research in the etiology, biology, diagnosis and treatment of breast cancer did not have anything significantly new to report, Gullino said. The presentations did, he said, point up the need for more work in such areas as the pathological history of mammary tissue, better evaluating the presence of metastasis, and the need to improve the life quality of the treated patient.

The reports on treatment research "need to be kept in perspective," Gullino said. "Bonadonna's trials have shown that the results for post menopausal patients are not very good. Fisher's results are still preliminary. It will be a couple of years before they produce useful information."

Here's what Gianni Bonadonna reported:

"When in operable breast cancer the axillary lymph nodes are histologically positive the disease should be considered as microscopically disseminated in the large majority of patients. A recent analysis carried out in our institute on 381 consecutive patients with involved axillary nodes confirms the progressive failure rate and the parallel decreased survival rate during the first 10 years from radical mastectomy not followed by postoperative radiotherapy.

"Since chemotherapy can be very effective on minimal residual disease after potentially curative surgery, the CMF adjuvant program was started on June 1, 1973, with the intent to improve both disease free period and survival in the high-risk group of operable patients. Within four weeks from mastectomy, 386 patients were randomized to receive no further therapy or 12 intermittent monthly cycles of CMF. The results updated as of July 1, 1976, con-

firmed that during the entire period of observation (average follow-up period for CMF 19.9 months, for controls 19.2 months), the probability of remaining free of disease was significantly greater for patients given combination chemotherapy compared to those treated only with surgery. Although the absolute recurrence rate is presently unknown, the difference in the relapse rate was particularly evident between patients with four or more nodes. The pattern of relapse was similar in both groups with preferential involvement of distant sites. Local-regional recurrence was observed in 13.3% of controls and in 3.3% of CMF patients. At the present moment, the difference in the survival rate is not significant.

"The experience achieved during the first 36 months of study indicates that CMF is a tolerable combination which proved to be useful in prolonging the disease free period in patients at high risk of relapse when treated only with local modality. Its effect on survival as well as its potential delayed toxicity require a long-term analysis."

Collaborating with Bonadonna in the study are A. Rossi, P. Valagussa, and U. Veronesi, all with the Istituto Nazionale Tumori, Milan.

Bernard Fisher, Univ. of Pittsburgh, reported on the National Surgical Adjuvant Breast Project studies, of which he is chairman:

"Despite effective loco-regional control, major improvement in survival has not occurred because all too frequently breast cancer is a systemic disease at time of diagnosis. Realizing the need to employ prolonged systemic therapy, a plan was devised in 1972 for such an undertaking. Based on kinetic studies, data derived from animal tumor models, as well as considerations regarding drug toxicity and patient and physician acceptance it seemed that a logical starting point for evaluating the worth of adjuvant chemotherapy in breast cancer would be to implement a first clinical trial utilizing a single agent (L-PAM).

"The aim was to progress in stepwise fashion, first comparing a single agent with no treatment, then two agents versus a single one and eventually three versus two. Hopefully, it could thus be ascertained what is required to attain a maximal therapeutic effect with acceptable toxicity. Moreover, such an approach might define subsets of patients who may be as responsive to single agents as to combinations. A specific aim of the first study was to ascertain whether L-PAM could prolong the disease free interval of patients. When that achievement was demonstrated, a progress report of findings was presented. Treatment was found to be advantageous, particularly for premenopausal women. With completion of patient entry into that protocol, patients were randomized between L-PAM and L-PAM plus 5-FU. By March of 1976, after 699 patients had been entered, patient entry was terminated. A new protocol comparing L-PAM plus 5-FU with L-PAM plus 5-FU plus MTX was implemented in June of 1976. More than 350 patients are currently being followed on that study."

Paul Carbone, Univ. of Wisconsin, reported on chemotherapy of advanced breast cancer by the Eastern Cooperative Oncology Group, of which he is chairman:

"The principles of combination chemotherapy include the use of effective single agents with non-pverlapping toxicities, inclusion of almost full doses, and utilization of intermittent treatment schedules. The resultant of these efforts has produced 50 to 70% response rates with complete responses in about 15 to 20% of patients. The duration of response has been about 10 to 12 months with corresponding increases in survival.

"Currently a wide variety of programs have been used primarily involving cyclophosphamide (C), methotrexate (M), fluorouracil (F), vincristine (V), adriamycin (A), and prednisone (P). In controlled clinical studies by ECOG, CMF produced responses in 49% whereas CMFP produced responses in about 63% of patients. Studies by CALGB have indicated a relatively better duration of response with CMFVP when compared to FVP. Studies by ECOG have also shown that CMF and AV are relatively equivalent with response rates of about 50% with no cross resistance. Several studies, particularly the Univ. of Arizona group, have studied AC with responses in the 70% range. Current approaches include the sequential use of combination CMF and AV, as well as the use of hormone or immunotherapies combined with various three and four drug treatments."

Kurt Brunner, Swiss National Cancer League, reported on combined chemo and hormone therapy in metastatic breast cancer:

"Chemotherapy and hormonal therapy act by a different mechanism and produce no overlapping toxicity. It therefore seems promising to combine both modalities of therapy in order to further improve the impressive treatment results achieved with combination chemotherapy during the past decade.

"Several studies are comparing either hormonal therapy alone with chemotherapy alone or combined hormonal—mainly oophorectomy—and chemotherapy with hormonal therapy alone.

"In a randomized Swiss study including 213 evaluable patients, a combination of hormonal and polychemotherapy was compared with polychemotherapy alone. Hormonal therapy was different for premenopausal or previously hormonally untreated or treated postmenopausal women.

"Forty-two premenopausal women were treated either with oophorectomy plus a modified five drug 'Cooper' combination or with the chemotherapy regimen alone. Oral methotrexate, cyclophosphamide and prednisone for two weeks was alternated with two week courses of i.v. fluorouracil, vincristine and prednisone. Nineteen patients treated with the

combined modality demonstrated a CR + PR of 74%, a minor PR of 16% and NC + P of 10%, versus 43%, 22% and 35% respectively in 23 premenopausal women receiving chemotherapy alone. Median time to progression was 9.5 months and median survival 19.9 months in the combined group, versus 7.8 months and 13.2 months respectively in the 'chemotherapy only' group.

"Ninety-six postmenopausal patients without previous hormonal therapy were treated with diethylstilbestrol and the same cytostatic therapy as described above (48 patients) or with chemotherapy alone (48 patients). CR + PR in the combined group is 63%, minor PR 21%, NC + P 16%, median remission duration 8.4 months, median survival 26.7 months. The corresponding results in the 'chemotherapy only' group are 54%, 25% and 21%, with 10.6 months median remission duration and 19.2 months median survival.

"Seventy-five postmenopausal patients with previous hormonal therapy, mainly oophorectomy (53 patients), received either chemotherapy plus a progestational agent (38 patients) or cytostatic drugs only (37 patients). Results in the combined group are: CR + PR 53%, minor PR 24%, NC + P 23%; median remission duration 8.9 months, median survival 18.1 months; in the 'chemotherapy only' group the corresponding figures are 63%, 11%, 27%, 10.0 months, 22.8 months.

"The results of the study favor oophorectomy combined with chemotherapy in premenopausal patients and, with certain limitations to be discussed, estrogens plus chemotherapy in hormonally untreated postmenopausal women. In a followup study we at present investigate the question, if postponing chemotherapy until response to hormonal therapy is established may further improve remission duration and survival."

Fisher also reported NSABP's trials comparing total and radical mastectomy and on the segmental mastectomy trial just getting started:

"Controversy exists relative to the proper operative treatment for female breast cancer. As a first step in an effort to resolve the dilemma, investigators from 34 member institutions of the National Surgical Adjuvant Breast Project participated in a protocol to compare alternative treatments of primary operable breast cancer with radical mastectomy. The specific aims of that study are to determine in patients without clinical axillary node involvement whether (a) total mastectomy is as effective a therapy for breast cancer as is radical mastectomy when patients having total mastectomy who subsequently develop significant palpable nodes have them removed and (b) total mastectomy with postoperative regional radiation is as effective a treatment for breast cancer as is radical mastectomy or total mastectomy with postponement of treatment until significant palpable nodes occur.

In patients with clinical axilllary node involvement, the primary aim is to ascertain whether radical mastectomy and total mastectomy with regional radiation are procedures which produce equivalent results. The 1,665 patients being followed were entered into the trial between August 1971 and August 1974. Those with clinically negative nodes (1,079 patients) were randomized into three treatment categories: radical mastectomy, total mastectomy and radiation, and total mastectomy alone. Clinically positive node patients (586) were randomized into two groups: radical mastectomy or total mastectomy with radiation.

At present, data reveal no significant difference in incidence of treatment failure or survival between the treatment groups in the clinically negative or clinically positive node patients. The average time on study is three years. Of considerable interest is the observation that 38% of patients in the radical mastectomy group considered to be clinically node negative were pathologically node positive. Consequently, a similar proportion of patients in the total mastectomy group could be expected to have had positive nodes left unremoved. Only 16% of those patients have required a delayed axillary dissection. Fifty-six of the 57 dissections were carried out $\leq$ 29 months following mastectomy; one was performed 49 months following operation.

"In June of 1976, the NSABP activated a protocol to compare segmental mastectomy and axillary dissection with and without radiation of the breast with total mastectomy and axillary dissection in a selected population of patients with breast cancer."

Samuel Hellman reported on trials involving treatment by radiation without mastectomy. Co-investigators were Martine Levene and Jay Harris, at the Harvard Medical School Joint Center for Radiation Therapy:

"One hundred and fifty patients with carcinoma of the breast were treated by radiation therapy without mastectomy. Sixty-three patients had excisional biopsy of the breast mass while the remainder had incisional biopsy or needle biopsy. There has been 100% local control in patients with stage I or stage II disease. The local control rate in stage III is 70%.

"The cumulative survival and relapse-free survival probabilities at five years are 100% and 91% for stage I, 71% and 59% for stage II and 31% and 19% for stage III."

Umberto Veronesi, National Cancer Institute of Italy, reported on "conservative" treatment in a Milan trial:

"The randomized clinical trial compares radical mastectomy with a more conservative procedure consisting of mammary resection plus axillary dissection plus radiotherpay. The resection comprises an entire quadrant of the breast together with the overlying skin and the corresponding portion of the fascial

sheet of the pectoralis major. The axillary dissection is performed in continuity with the resected breast quadrant except in cases with tumors of low inner quadrants, who need two separate incisions.

"After surgery the patients receive 6,000 rads to the residual breast tissue over 5-6 weeks, starting 15 days after operation. The costmetic results are satisfactory in approximately 70% of the cases. The trial is limited to cases with tumors less than two centimeters and no palpable axillary nodes. Patients with histologically positive lymph nodes are submitted to adjuvant chemotherapy with CMF for one year.

"From September 1973 to September 1976 324 cases entered the trial. One hundred sixty were treated with radical mastectomy and 164 with the conservative procedure. Axillary metastases were found in 21% of the radical and in 25% of the conservative surgery group. Four loco-regional recurrences have occurred till now, two in each group. Four cases in the radical mastectomy group had distant metastases. The clinical trial will collect some 500 cases by the end of 1977 and significant preliminary results are expected to be available from 1978."

Jan Stjernsward, Swiss Institute for Experimental Cancer Research, reported on adjuvant radiotherapy trials:

"Adjuvant radiotherapy in breast cancer according to stage of disease present therapeutic advances and the biology of the tumor is summarized:

"Stage I. The increasing number of small localized tumors accurring with earlier diagnosis motivates controlled clinical studies of irradiation of the breast with surgical axillary lymph node status for exact biological classification. Encouraging results with local breast irradiation prioneered mainly from France needs confirmation in such controlled studies. Improved survival by interventions locally will most probably be due to selection of cases with earlier diagnosis rather than to variations in local therapies.

"Stage II. Pre-operative irradiation trials are biologically not logical in patients who are strictly operable and with a high risk of occult dissemination at time of irradiation. Adjuvant half body or total body irradiation to very high risk stage II patients may now be logical to explore in controlled studies.

"Identification of the very limited sub-groups of patients who will benefit from radiotherapy in stage II is open for trials. The routine use of post-operative irradiation in strictly operable patients is highly questionable. In spite of a demonstrated decrease of local and regional recurrence and the psychological trauma of discovering a local growth, the following four facts weight heavily against the routine use of post-operative radiotherapy.

"1. Overtreatment: (a) less than 10% have local-regional recurrence without distant metastases. (b) in the ca 25% who get local recurrences, a watch policy with later radiotherapy gives complete local control in 70%.

"2. Increased morbidity: besides a local-regional morbidity an increased mortality (+1 to 10%) can be correlated with the use of radiotherapy in 8/9 randomized trials.

"3. Systemic therapies: the logical way to improve survival. Multiple drug chemotherapy has been shown to be most effective against soft tissue metastases. It can not be excluded that radiotherapy diminishes the effect of systemic therapies (chemo-hormone or immunotherapy).

"4. Social-economic aspects: the patient's time and money, doctor's time and society's resources may be better used. Priorities are necessary even in oncology.

"Stage III. Radiotherapy has a clear therapeutic role in inoperable tumors limited to the breast. Its exact role in synergism with systemic therapies in a multiple modality approach remains to be precised in controlled studies.

"Stage IV. A palliative effect is well established. Controlled studies are lacking analysing whether there is a cost-benefit ratio that is advantageous when compared to more simple forms of therapy. The indicated positive effect of half body/total body irradiation is open for a controlled trial."

Luther Brady, Hahnemann Medical College, discussed the role of postoperative radiation therapy:

"The survival pattern for five-year periods 1940 to 1969 indicate that patients continue to die of their disease up to 15 and 20 years after diagnosis. Proper management of early stage disease remains an enigma despite repeated clinical studies of alternative treatment techniques. With the advent of more effective screening techniques, more patients are being shown to have disseminated disease at the time of initial diagnosis, clinically unsuspected. From these data, major factors have emerged which allow for the prediction of the ultimate survival of the patient with breast cancer.

"The successful treatment for breast cancer must be measured not only by survival but by local and regional control of the disease process. Local treatment, whether surgical, radiotherapeutic, or a combination of both, only influences the disease process within the treated area and can have no significant effect on occult distant metastases already present at the time of the initial treatment. Local treatment can, however, control disease on the chest wall and in the regional lymphatics of the breast. The role of radiation therapy in the management of carcinoma of the breast varies widely depending upon the extent and the rate of progression of the disease. Freedom from local-regional tumor is of immeasurable benefit to patients whose quality of life is thus profoundly improved.

"Continued evaluation of therapeutic modalities available for the treatment of carcinoma of the breast has failed to answer basic questions. Data are now

available to support the need for postoperative radiation therapy in selected groups of patients. Waiting until there is local or regional recurrence of breast cancer only allows for associated dissemination of the disease. The majority of patients presenting with chest wall recurrence also have disseminated disease at the same time.

"It must be emphasized that selection in almost all series blurs the results. Therefore, caution is mandatory in their interpretation. The ultimate appropriate treatment program in light of the data presently available may prove to be surgery, postoperative radiation therapy, and long-term chemo prophylaxis."

TASK FORCE TO EVALUATE RESPONSES TO RFPs AT JAN-MARCH-MAY MEETINGS

The meetings every two months of the Breast Cancer Task Force, initiated by Pietro Gullino when he became chairman last year, will continue with a modified schedule next year.

Gullino said the meetings in January, March and May will be "our major efforts in selecting projects to be funded" from the massive number of proposals generated by Task Force RFPs. Gullino said there has been "a tremendous response" to the RFPs issued this year, and they are still coming in. The final deadline for receipt of proposals to some RFPs is in February.

The July and September meetings next year will be devoted to "thinking up new projects," Gullino said. The November meeting may be eliminated, left to each committee to decide if it wants to meet. The format for all but November will be the same—the first day for reports from BCTF contractors, the second day for committee meetings.

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 noted.

RFP NO1-CM-77129

Title: *Development of pharmacuetical dosage forms*
Deadline: *Feb. 15*

NCI requires research efforts involving development of intravenous dosage forms of potential antitumor agents. Investigations will be directed toward resolution of complex solubility and stability problems associated with certain compounds of interest to the Cancer Program.

Organizations must submit evidence of in-house competence and resources in pharmaceutical development of parenteral products. Emphasis will be placed on awareness of the problems and the approaches to their resolution.

Contract Specialist: C. Lerner
Cancer Treatment
301-427-7463

RFP NCI-CM-77130

Title: *Preformulation and production of investigational dosage forms*
Deadline: *Approximately Feb. 15*

NCI requires a pharmacuetical facility for the preformulation dosage forms of potential antitumor agents. The products for development will primarily involve sterile lyophilized injectable dosage forms for use in preclinical trial in large animals and subsequent clinical trial in man.

Most production assignments will require preparation of lyophilized batch sizes between 1,500 and 6,000, 10 ml. vials. Chemical, physical and biological testing on all finished dosage forms will be required. organizations must submit evidence of in-house competence and resources.

Contract Specialist: J.A. Palmieri
Cancer Treatment
301-427-7463

SOLE SOURCE NEGOTIATIONS

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

Title: Large scale tissue culture production of tumor viruses
Contractor: Pfizer Inc.

CONTRACT AWARDS

Title: Statistical center for Tyler asbestos workers' program
Contractor: M.D. Anderson, $324,276.

Title: Chemical characterization of purified thymic products of other agents promoting lymphocyte differentiation
Contractor: Yale Univ., $70,199.

The Cancer Letter—*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.