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DEVITA SAYS HE DID NOT AGREE TO INCLUDE "CHOP-LIKE" ELEMENTS IN CCOP RFA BUT THAT HE WOULD CONSIDER IT

NCI Director Vincent DeVita did not agree that "CHOP-like" cancer control elements would be written into the initial RFA for the Community Clinical Oncology Program, as reported last week in *The Cancer Letter*. "I said that we can include it but I didn't mean we definitely would," DeVita explained. "I meant that we would consider it, and we are."

Everything that has been suggested by the variety of groups—the National Cancer Advisory Board's Cancer Control & Community Subcommittee, the Assn. of Community Cancer Centers and its Clinical Research Committee, the Board of Scientific Counselors of the Div. of Resources, Centers & Community Activities and its Subcommittee on Community Oncology & Technology Transfer, and participants at workshops—will be considered, DeVita said. However, the final RFA will not contain everything that everyone wants, he warned.

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In Brief

HAMMER HEARS A CLAIM FOR THE $1 MILLION; WYNDER'S THEORY ON JAPAN'S COLON CANCER RATES: HAMBURGERS

ARMAND HAMMER, describing one response he received to his offer of $1 million to anyone who comes up with a "cure" for cancer comparable in effect to Jonas Salk's polio vaccine: "A fellow came to my house in Los Angeles one night and said he had come to collect the million dollars. He had the cure, he said. It was in a book he had written on nutrition." . . . ERNST WYNDER (who also might lay claim to the prize on the strength of his early efforts on cigarette smoking) suggested as one reason why Japan may soon experience rising colon cancer rates: the growing popularity there of American hamburger franchises. "We sell them hamburgers, they sell us Toyotas and Sonys and we wonder why we have a negative trade balance," Wynder said. . . . GYNECOLOGIC ONCOLOGY symposium will be presented March 25-27 by the Johns Hopkins Univ. Gynecologic Oncology Dept. at the Hyatt Regency Hotel in Baltimore. An update on the biology of cancer; principles of surgery, chemotherapy and radiotherapy, and the current status of the evaluation and support of the gynecologic patient will be presented. Contact Program Coordinator, Continuing Education, Turner Auditorium Rm 22, 720 Rutland Ave., Baltimore 21205, phone 301-955-6046. . . . GARY WILLIAMS, associate director of the Naylor Dana Institute for Disease Prevention, the research component of the American Health Foundation, received the Arnold Lehman Award from the Society of Toxicology. The award was in recognition of Williams' contribution to the understanding of mechanisms of action and detection of chemical carcinogens.

DEVITA FEARS INCLUDING CONTROL IN CCOP WOULD REDUCE THEIR NUMBER

(Continued from page 1)

The final RFA (request for applications) will not be written until after the NCAB gets one last crack at the program during its May meeting. Unless the Board rejects the recommendation of its subcommittee, it will advise DeVita to include some provision for cancer control in CCOP.

Subcommittee Chairman Gale Katterhagen presented a strong argument for including some of the cancer control projects which make up the Community Hospital Oncology Program when the subcommittee met earlier this month. DeVita said then he was impressed by Katterhagen's logic, but suggested that the increased cost each CCOP would incur by adding elements other than clinical trials would result in fewer of them being funded.

"The essence of CCOP is that we would have enough of them to reach around the country and make participation in clinical trials available to every area," DeVita said last week.

The CHOP-like elements which Katterhagen said should be considered include projects in prevention, detection, continuing care, terminal care, bereavement counseling. "Clinical trials have the best chance of getting the physicians to participate, if the physicians are already involved in programmatic activities like those," Katterhagen said.

NCI staff prepared a brief history of the development of CCOP and how it was perceived by NCI at the time of Katterhagen's subcommittee meeting. Much of the information it contains has been previously reported, but this document pulls it all together. The report follows in full:

COMMUNITY CLINICAL ONCOLOGY PROGRAM

In March 1981 the director of the National Cancer Institute announced interest in establishing a large scale cancer control effort to involve practicing community oncologists in the NCI clinical trials programs. The purpose of the program is to develop a network that would utilize the resources of the increasing number of highly trained oncologic specialists in the community who have entered practice in recent years. Coupling such a network of practicing oncologists with ongoing clinical research projects would result in a sustained entry of patients to clinical studies. Improvements in cancer management for all cancer patients would be achieved more expeditiously.

In reponse to this announcement, the Assn. of Community Cancer Centers established a Committee on Clinical Research. Recommendations from a series of deliberations, with advice from 55 health professionals representing communities in 20 states, were presented to NCI, with extensive documentation.

In July 1981 the Board of Scientific Counselors of the Div. of Research, Centers & Community Activities formed a Subcommittee on Community Oncology & Technology Transfer chaired by Dr. Charles Moertel. Deliberations of that subcommittee included academic and community oncologists, cancer center directors and cooperative group chairmen. The position paper developed by this subcommittee was presented to the DRCCA Board of Scientific Counselors, which gave concept approval for the Community Clinical Oncology Program in October 1981.

Subsequent program planning and development of a request for applications has been the responsibility of an NCI CCOP working group which includes the director, DRCCA; deputy director, NCI; associate director, Cancer Therapy Evaluation Program, DCT; and representatives of the Clinical Investigations Branch, DCT; and the Community Outreach & Rehabilitation Branch, DRCCA. Dr. Jerry Yates, an experienced and widely respected clinical oncologists, will be joining NCI in mid-April as associate director for Centers and Community Oncology, DRCCA. Dr. Yates will take primary responsibility for CCOP.

The CCOP working group continues to receive suggestions on CCOP. These have included, since Jan. 1, 1982, presentation to the National Cancer Advisory Board, the Board of Scientific Counselors, DCT, the American Assn. of Cancer Institutes and a regional workshop for community oncologists in Los Angeles. Further workshops are planned with the clinical cooperative groups, subcommittees of the NCAB and DCT Board, as well as additional regional workshops for community oncologists in March and April 1982.

Objectives of the CCOP Program

(1) To bring the advantages of clinical research to cancer patients in their own communities, by having practicing doctors and their patients participate in clinical treatment research protocols, and thus foster a dynamic continuum between clinical research and cancer control.

(2) Reduce national mortality by speeding the transfer of advanced treatment technology to widespread community application.

(3) To provide a sound cancer control research basis for investigating the diffusion of cancer therapy throughout medical practice, based on participation in clinical research studies. The diffusion hypothesis presumes that introduction of quality controlled clinical research trials in the community should result in benefit as well to those patients not treated as part of a protocol.

(4) To develop programs to serve as part of a nationwide network for quality controlled distribution of experimental anticancer agents.

(5) To create a network that could be used as a resource for future NCI-sponsored cancer control and prevention research activities.

Clinical Trials Research & Community Medicine: Background for a New Dynamic Relationship

In this country, over 80 percent of patients with cancer are treated in community hospitals and clinics close to their homes. The remainder are treated in university and government hospitals and cancer centers. Currently, the Div. of Cancer Treatment supports a national clinical trials program, largely through academic centers. These have included (1) multimodal national and regional cooperative groups, (2) groups in which the investigators have a particular expertise (such as pediatricians), (3) groups that are designed to deal primarily with high technology, single modality studies and (4) groups that are specifically disease oriented. Additional large cancer centers are involved in implementation of local clinical research protocols.

The past decade has seen increasing numbers of highly trained clinical cancer specialists, experienced in clinical research and protocol care, enter private practice in the community. Thus, there are highly qualified professionals in the community capable of participating in clinical research. Experience within several cooperative groups has indicated that cancer physicians in community practice produce clinical research data of similar high quality to that of the academic centers. Evidence thus exists that new technology can be transferred in a dynamic interactive way by having community

physicians participate in clinical research. This initiative is intended to meet the needs of cancer patients by utilizing the trained specialist now practicing in community hospitals and clinics and establish a system of community clinical oncology programs, with national distribution which will participate in clinical trials research.

This program will be developed and supported by the Centers & Community Oncology Program, Div. of Resources, Centers & Community Activities. Participating programs will be required to enter or refer a minimum of 50 evaluable patients annually into NCI approved clinical trials and must be prepared to enter approximately 10 percent of patients available to them to clinical trials designated as high priority by the research base with which the CCOP is affiliated. These research bases may be national or regional cooperative groups, specialized cooperative groups, or cancer centers currently participating in NCI approved, clinical research protocols.

Participants are encouraged to enter or refer, if appropriate, patients with uncommon cancers. Patient entry onto clinical trials will be done through collaboration with one or two primary multimodality research bases having a spectrum of clinical trial protocols available and, if desired, through one or more specialty research bases. Eligible patients in a single disease category should be allocated to one protocol in the case where multiple affiliations have resulted in overlapping protocols.

The diffusion hypothesis will also be tested during the course of the program. According to this hypothesis, one anticipates that by having a fraction of patients participating in research, there will be a benefit that will extend to those patients who are not participating in research protocols. Evaluation projects separate from this procurement will address the testing of this hypothesis. It is also an aim of this program to develop a participatory process for setting goals in order to decrease national mortality in disease sites in which effective therapy exists. Community Clinical Oncology Programs should be aware that they may be asked to participate in future cancer control programs of the NCI. Furthermore, applicants should consider whether or not they have an interest in participating in additional NCI sponsored cancer control and applied prevention research programs.

Qualifications for Award

A Community Clinical Oncology Program may be a single clinic, a group of practicing physicians, a single hospital, or a consortium of physicians and/or clinics and/or hospitals. The consortium approach is necessary when several such community cancer treatment resources serve the same patient catchment area. Only one of multiple CCOPs competing for the same patient population will be approved.

National Cancer Institute recognized comprehensive and clinical cancer centers (holding core grants) are not eligible, and university hospitals will be restricted to those participating as part of a consortium or those operating as community hospitals in which private practice oncologists provide treatment. In the initial phase of this program, university hospitals participating as cooperative group members will not be eligible. Those institutions that currently participate as part of the Cooperative Group Outreach Program or Cancer Centers Outreach Program would be eligible.

CCOP Obligations for Entry of Patients on Cancer Clinical Research Protocols (the "Tithe")

Each Community Clinical Oncology Program must have a demonstrated potential and stated commitment to contribute a minimum of 50 evaluable patients per year to approved clinical research protocols active in the center or group with which the community center is affiliated. The written affiliation agreements between the CCOP and its research bases will specify the priority protocols which can meet this obligation. As one measure of performance, it is expected that approximately 10 percent of patients available to physicians in a CCOP will be placed on protocols. If patients must be transferred from the community to a specialized center in order to receive treatment according to protocol, appropriate weighted credit would be given.

CCOP Linkage to Research Bases

Each Community Clinical Oncology Program must have evidence that an affiliation has been established with a nationally recognized clinical cancer research base. A list of research base options is provided as an attachment to this program description. These may be clinical or comprehensive cancer centers, national or regional cooperative groups. Multiple affiliations may be permitted provided the issue of overlapping protocols is adequately addressed. This should be a part of the written agreement between a CCOP applicant and corresponding research bases at the time of proposal submission.

Quality controlled clinical research data is a performance requirement. Assurance of quality is the joint responsibility of the CCOP and its research base affiliates. Quality control procedures, operational in the center or group, will be applied to the CCOPs and must be specified in the CCOP-research base affiliation agreement.

Funding of the Community Clinical Oncology Program

The CCOP is scheduled to begin in fiscal year 1983. In the fully developed program, NCI is prepared to fund CCOP up to a total cost of $10 million per year. Initial awards will be based on the number of qualified, acceptable proposals received. CCOP awards will be made directly to the community programs. Allocation of CCOP funds to support the cost of receipt, handling quality control assurance and analysis of patient data by the affiliated research bases should be mutually agreed upon and specified in the written agreement between the CCOP applicant and its research base. Awards will be in the form of cooperative agreements, now the preferred mechanism for funding NCI clinical trials programs.

CCOP is intended to be a long term NCI program to involve community oncologists in high priority cancer clinical trials. Individual programs will be expected to apply and pass merit review for competitive renewal every three-five years.

Location of the CCOP workshop in the Chicago area, not determined when the workshop schedule was first announced (***The Cancer Letter,*** Feb. 26), is as follows:

April 13, Northwest Community Hospital, 800 W. Central Rd., Arlington Heights (near O'Hare Airport). The time will be announced next week. Contact Margaret Stewart, Illinois Cooperative Network, 312-346-9813. Reservations are required due to limited space.

Other workshops are scheduled for Dallas, March 19, St. Paul's Hospital, 1-3 p.m.; Newark Airport Holiday Inn, March 23, 10 a.m.-1 p.m.; New Orleans, Ochsner Clinic, March 26, 1-3 p.m.; Orlando, April 3, Sheraton Hotel, 1-3 p.m.; Boston April 6, New England Deaconess Hospital, time to be announced; Atlanta, April 20, South Fulton Hospital, time to be announced.

ADJUVANT NUTRITION IN BREAST CANCER STUDY OFFERED TO COOPERATIVE GROUPS

NCI is planning to propose to the cooperative groups that they consider initiating controlled clinical

trials with stage 2 postmenopausal breast cancer patients to evaluate dietary intervention as a form of adjuvant therapy.

The study was recommended by Ernst Wynder, president of the American Health Foundation, to the Div. of Cancer Treatment Board of Scientific Counselors.

Wynder offered to conduct the trial himself, with patients from New York area hospitals. But some Board members objected to creating another clinical trials group when the cooperative groups are available to do large scale studies. They also expressed doubt that a group limited to the New York area, or any other single city, could accrue enough patients—Wynder suggested 400 plus 400 controls. All patients in the study, including controls, would have to receive the same chemotherapy regimen following surgery.

A "white paper" on the scientific rationale for the study will be presented to group chairmen and to the chairmen of each group's breast cancer committee by the Cancer Therapy Evaluation Program of DCT. CTEP will suggest that those groups interested in developing such a study contact Wynder and collaborate with him, if they feel they need nutritional expertise.

Wynder briefly described the rationale for the study in his presentation to the DCT Board:

"Based on the fact that longer survival rates for breast patients are found in countries and regions within countries with characteristically low breast cancer rates, compared to areas with high rates, it has been suggested that the same variable which influence tumor induction may also affect the subsequent course of the disease in the host. In this context, several retrospective studies correlating such risk factors as reproductive history, family history of breast cancer and obesity and either disease free survival or overall survival have recently been reported.

"Interest in obesity and/or dietary fat as important determinants of survival after surgery is based on the fact (1) that a large body of epidemiological and experimental evidence suggests that high fat intake, and to a less consistent extent, obesity, are important determinants of breast cancer risk, and (2) that both variables are amenable to modification by dietary means. A positive association between obesity and increased risk of breast cancer has been reported by some but not other investigators. In animal models, obesity also increases the incidence of breast cancer, but appears to do so independently of high fat intake. Whether this is the case with regard to human breast cancer remains to be determined. With regard to survival, Donegan, Tartter, Abe, Boyd and others have shown that obese breast cancer patients have a greater chance of early recurrence and a shorter five year survival period than nonobese patients. However, Donegan in another study, and Schrabi, reported no association between obesity and disease free period or overall survival. The reason for this inconsistency is uncertain. Factors such as sample size, differing definitions of obesity, differences in control populations, and differences in the nutritional basis of obesity, could contribute to the inconsistent results obtained. It is noteworthy that the effect of obesity, as observed by Tartter, was principally apparent in conjunction with high serum cholesterol levels.

"The concept that dietary fat—as an etiological factor distinct from chemical contaminants of the diet and other environmental and genetic factors—is an important determinant of breast cancer risk is reinforced by a variety of epidemiological and laboratory animal studies," Wynder continued. "With few exceptions, the bulk of epidemiological evidence suggests that total fat intake is an accurate index of risk, particularly among postmenopausal women, where incidence rates are highest. Moreover, laboratory animal studies conducted over the past 40 years in spontaneous, chemically induced, transplantable, and radiation induced mammary tumors have demonstrated unambiguously that high fat intake promotes the development of mammary cancer.

"The precise mechanism(s) by which dietary fat exerts its tumor promoting effects are still being debated. Postulated mechanisms by which dietary fat may influence breast cancer fall into two basic categories, namely, those involving direct effects of fat on tumor development and those involving indirect effects on host metabolism. Direct effects involve changes in (a) the lipid content of the cell membrane and/or membrane bound receptors, and (b) the synthesis of prostaglandins (biologically active derivates of the essential fatty acids, arachidonate and linoleate). Indirect mechanisms involve (a) subversion of the immune system, (b) stimulation of mixed function oxidase systems involved in carcinogen activation or steroidogenesis, (c) alterations in fecal flora and bile acid metabolism, and (d) alterations in the endocrine milieu of the host.

"If the hypothesis that the same factors that affect tumor induction also influence overall survival is correct, then a reduction in dietary fat intake following mastectomy should result in an objective increase in disease free survival and overall survival in breast cancer patients. Since retrospective analyses of the relationship between survival after mastectomy and dietary fat intake are precluded by the absence of adequate dietary histories in the present patient file, and since experimental animal studies are impeded by the absence of reliable models of recurrent metastatic mammary cancer, it is proposed that a randomized prospective clinical trial is the most feasible and direct experimental mechanism by which to test the hypothesis that dietary fat acts as an important determinant of survival after mastec-

tomy in postmenopausal breast cancer patients.

"The objective of the present proposal, therefore, is to determine whether a low fat, high complex carbohydrate diet can serve as an effective form of adjuvant therapy in postmenopausal breast cancer patients. To this end, breast cancer patients will be randomized shortly after surgery. Both groups will receive similar chemotherapy regimens. However, and in addition, the control group will consume its customary diet. This diet characteristically consists of 40 percent of calories as fat with a polyunsaturated-saturated-monounsaturated P/S/M ratio of 0.4:1:1. The experimental group will consume a modified diet based on the Japanese model consisting of 20-25 percent of calories as fat with a P/S/M ratio of 1:1:1. The trial will be limited to postmenopausal patients with stage 2 disease (lymph node involvement), since this is the patient subset which has been shown to be the most resistant to chemotherapy and which is most likely to respond to dietary adjuvant therapy.

"The endpoint—tumor recurrence—will be assessed by clinical examination and conventional diagnostic methods such as chest x-ray and bone scans. Disease free survival rates in the two groups will then be compared by actuarial analysis over a five year period.

"The significance of this proposal lies in the fact that it will provide necessary information regarding the possible utilization of a novel treatment strategy, namely the use of dietary intervention as a form of adjuvant therapy for breast cancer patients. Equally important, it will focus on that subset of the breast cancer population which, though the largest numerically, is the most intractable with regard to more conventional therapeutic procedures, namely postmenopausal women; and lastly, such a trial may bring clinical oncologists one step closer to the goal enunciated by Carter of a 'totally effective, nontoxic therapy' for breast cancer patients."

Wynder estimated the study would cost $600 per patient per year.

Board Chairman Samuel Hellman noted that the trial, since it would involve extensive monitoring, would require that patients be located in the New York City area if Wynder did the study.

"I would like to do this myself as much as possible," Wynder said. "This is the most important lead I've had other than smoking."

"Why not try it with a well written grant?" Hellman asked. "A half million dollars a year is well within the province of a conventional R01."

"We need innovative methods to treat breast cancer," Wynder said. "We believe the evidence is significant for nutrition intervention. I would like to get the support of this Board in terms of concept, and leave it up to Dr. [Bruce] Chabner and Dr. [Vincent] DeVita to tell us the way to go."

Board member Philip DiSaia questioned whether the study could be "controlled enough to get quality data. . . . The issue isn't the idea. It's great. The issue is, can you prove it?"

"Time out," Hellman interjected. "This is not a site visit. The question is, is this idea provocative enough for us to advise Dr. Chabner [DCT acting director] to provide support in a special way. It is not fair to ask Dr. Wynder to provide us with detailed information to support a grant."

"The questions are, is there scientific evidence that obesity has an influence on breast cancer, and is there a mechanism to do the study," Board member Theodore Phillips said. "The cooperative groups could do it."

"The suggestion is, there are existing cooperative groups doing randomized studies with stage 2 postmenopausal breast cancer, and they be invited to do this study," Hellman said. "Is that acceptable?"

Wynder said he had discussed the study with Bernard Fisher, chairman of the National Surgical Adjuvant Breast Project, who said his group would have to hire nutritionists and others to undertake such a study.

"I agree the study is feasible," Board member Sydney Salmon commented. "The cooperative groups could do it. The major issue is whether the science is at the point where this Board can recommend special funding. Stronger evidence would be helpful."

"The evidence presented is certainly sufficiently exciting to warrant a study," Board member Sharon Murphy said. "It is not necessary to hold up a trial until more evidence is in. I disagree violently with Ted, that the cooperative groups is the way to do it. With the cooperative groups, the study would be inconclusive and worthless. This needs someone with enthusiasm and the charisma to help women on a diet."

Murphy offered a motion recommending that "some special mechanism be established to expedite the study. . . . I'm afraid that with an R01, it would not get a fair review from a study section."

Chabner said that if a regular grant proposal were to be submitted, "it would be reviewed by an appropriate [NIH-DRG] study section, one probably that would include an epidemiologist and a nutritionist, and I think the review would be just as capable as it would be if we did it, maybe better. Another mechanism would be a sole source contract. To do that, we would have to make the argument that his [Wynder's] institution is uniquely capable of doing the study."

"I'm upset at the idea of running off and setting up another special contract group," Phillips said. "Special contract groups have not been successful in the past. We have the cooperative groups, they're good, and can do these studies. Maybe Bernie Fisher's

group does not want to do it, but then we need to give ECOG, SWOG, and others the opportunity. They can do it, and cheaper."

William Maguire, M.D. Anderson, who was present at the meeting, said, "I'm 100 percent convinced that you can't do a study with 400 patients, stage 2, postmenopausal, and have the variables controlled well enough to obtain meaningful data."

"If what you are saying is true, then we can't have CCOPs either," Murphy said.

DiSaia offered a motion asking that NCI "explore all avenues to support the project."

"That would be okay," Murphy said, "but I am concerned about making this wide open to the cooperative groups. Not that they don't do good clinical trials, but this project needs someone with expertise in nutrition."

"I think Dr. Wynder should initiate an R01 or sole source proposal," Board member Susan Horwitz said. "All we have to do is to say we're enthusiastic about it. Bruce knows how we feel."

"Let's leave it at that," Hellman said.

Phillips offered a motion to refer the proposal to CTEP staff with the suggestion that it be brought to the attention of the cooperative groups.

"Some members do not agree that the groups should do this," Hellman said. "Everyone knows how we feel." None of the three motions was brought to a vote.

CTEP staff subsequently concluded that the study would require participation of multiple institutions and that the groups offer the best approach. With Wynder's availability to provide nutrition expertise (and the prospect of additional NCI funds to pay for it), the decision was made to submit the proposal to the groups.

NCI AGREES TO LIFT LIMIT ON SURGERY PLANNING GRANTS ON DCT BOARD REQUEST

Seventy-nine grant applications in surgical oncology are being reviewed this month, the response from an RFA offering support for exploratory studies and a program announcement aimed at stimulating R01 and program project grant applications in research on the surgical treatment of cancer (***The Cancer Letter***, June 26, 1981).

Three are program projects, with budget requests totaling $2.1 million; 51 are R01s, requesting $4.4 million; and 25 are exploratory or planning grants (P20s), asking $2.5 million.

The new effort in surgical oncology was initiated by the Div. of Cancer Treatment Board of Scientific Counselors, which approved the concept last year on the recommendation of its Surgical Oncology Research Development Subcommittee (SORDS) chaired by Walter Lawrence.

Lawrence, whose term on the Board has expired, appeared at last month's meeting to report on a workshop organized by SORDS and to object to the limit NCI placed on the number of planning grants it intended to award in the new program. The RFA said NCI intended to award "approximately five" grants "if sufficient meritorious applications are received." Awards may not exceed $100,000.

"I was shocked to see that limit in the RFA," Lawrence said. "That was not SORDS' idea. If there is no reconsideration, surgeons will say this is a lot of hooey. This is subverting the Board's intention."

DCT Acting Director Bruce Chabner said it would be possible to increase the number of awards. "The problem is the financial situation. We didn't know what the response would be. It was considerable."

Board members offered various motions—to remove the limit, to fund a minimum of eight, and to fund planning grants up to 30 percent of the total amount of money which will support the program project and R01 grants. No votes were taken on any of the motions.

"We could leave the figure at $500,000, but fund any others that come in under the payline," Chabner said. Board member Gertrude Elion offered that as a motion, with Chairman Samuel Hellman's addition, "If it goes over $500,000, you will come back to us for advice on where the additional money should come from."

That motion was approved, thus opening the way for more of the 25 P20 applications to be funded—all those, in fact, which score at or below the priority score payline.

Lawrence said that SORDS also recommended the subcommittee be continued (Hellman agreed and appointed Philip DiSaia as chairman) and that NCI upgrade the position within DCT which supervises extramural programs in surgical oncology. That position now is the surgery section (along with Medicine, Nutrition and Pediatrics) within the Clinical Investigations Branch of the Cancer Therapy Evaluation Program. "That ought to be at the branch level," Lawrence said.

Lawrence presented a summary of the workshop, which focused on melanoma, breast cancer, colorectal cancer, and soft part sarcoma:

Melanoma discussions led by Charles Balch and Wallace Clark made a number of recommendations regarding needed histologic "measurements" in addition to the current and standard microstaging methods. These were clearly important data to be recorded for all future prospective trials in order to determine prognostic significance of these pathologic features and related assays. The regional management discussions by Harold Wanebo and Charles McBride focused on an intensive review of the status of elective regional node dissection and the current basis for regional perfusion chemotherapy of melanoma. Although a minority of participants felt that two clinical studies of elective lymph node dissection clearly settled the issue, the majority believed further investigation of regional lymph node dissection was needed for melanomas of intermediate thickness, and such a study or studies should include the histologic evaluation outlined earlier by Clark.

Some differences of opinion developed when regional perfusion was discussed, but the consensus was that regional perfusion chemotherapy (with or without hyperthermia) still needs to be established for melanoma by clinical trials using a control group receiving systemic therapy. Other regional therapies (intralymphatic isotopes and chemotherapeutic agents, regional heat, intralesional immunoadjuvants, etc) were also discussed as lower priority projects.

The **breast cancer** presentation was chaired by Richard Wilson. Robert Hutter described the current AJC system as the standard staging system to be employed in future surgical trials. The group expanded the necessary information to be recorded for expanding information on potential prognostic factors. Bernard Fisher and William Donegan discussed regional management research concepts that might be explored at this time. It appeared that the major local treatment principles are now being tested by ongoing clinical trials and further biologic and therapeutic questions need to await the answers obtained. Donegan offered several alternative therapeutic trials for management of regional disease in stage 1 and 2 breast cancer patients. He proposed that the optimal therapeutic strategy for preinvasive cancer, therapy of stage 3 breast cancer, and breast "salvage" operations be studied as well. The consensus regarding studies of regional approaches to breast cancer was that new alternative treatment choices for the regional therapy of breast cancer was not a high priority at this time, but a more detailed recording and analysis of many possible prognostic factors would be valuable. The group felt that new biologic questions to be asked after current trials are completed are unlikely to be related to regional treatment alone.

The **colorectal cancer** session chaired by Jerome DeCosse dealt with staging initially as well as the key pre- and post-treatment data to be reported in all future clinical studies. The factors considered important coincided with the data set considered critical by the recent workshop on this subject in Brisbane, Australia. Oliver Beahrs presented staging in the AJC TNM format, adding additional important clinical and pathologic observations (including biologic markers). It would appear that the specific components of the staging system are more important than the actual nomenclature of the staging system employed, but the AJC system is a useful foundation on which to build data in our future clinical studies.

Arthur Aufses carefully dissected many local principles that might apply to treatment of colorectal cancer. However, after extensive analysis and discussion it was the consensus of the group that few if any of these local treatment modifications (bowel preparation, extensive lymph node dissection, importance of local margins, special handling of remaining bowel, oophorectomy, etc.) merited clinical investigation since no new information on the nature of colon cancer would be obtained. Adjuvant radiation or chemotherapy to the liver and possibly other adjuvant trials were considered more important at this time than regional modifications in the treatment.

Harry Sears' discussion of the standardization of the operative details and record keeping for clinical trials clearly demonstrated a need for such standardization if systemic clinical trials are to be meaningful. Uncontrolled variations in the operative resection could easily affect outcome more than variables being manipulated. Standardization of operative procedures was also considered an essential objective for future clinical trials of other cancers in which operation is employed.

The session on **soft part sarcomas**, chaired by Lawrence, began with a staging schema presented by William Russell. As with the other neoplasms discussed, the basic staging is the AJC system (which includes histologic grade as an important factor) along with the added factors of histogenetic site of origin, lymphatic metastasis, anatomic site, and patient age. Standardization of nomenclature of the operation employed for soft part sarcomas was also accomplished, but there was no consensus regarding need for trials of local or regional treatment. Specifically, there was limited enthusiasm regarding a clinical trial to determine the value of adjuvant radiation therapy in patients receiving adequate resection with reasonably wide margins.

Franklin Sim and Steven Rosenberg presented points of view on the regional therapy of soft part sarcoma and in both presentations it was apparent that a part of the difficulty in establishing treatment protocols for optimal regional therapy was that there were many small subgroups of sarcoma due to heterogeneous presentations. Lawrence expressed concern that the true role of adjuvant radiation for this group of neoplasms had not been clearly established. The only consensus regarding treatment was the need for confirmation of the early and encouraging data on adjuvant chemotherapy for soft part sarcoma in adults (reported by Rosenberg) and it was felt that additional trials could utilize much of the staging and classification data discussed earlier.

General Conclusions:

1. A uniformly agreed upon staging system is mandatory for all future clinical trials utilizing operation as a major part of the therapeutic strategy and the AJC staging systems serve as a good minimum data base for this purpose. However, for each neoplasm many additional data that were discussed need to be recorded in prospective fashion to allow development of additional information on the natural history and prognosis of these cancers.
2. For all new clinical trials involving operations, standardized protocols for both pre-treatment information and the operation itself must be developed with data forms designed to monitor these factors.
3. Whereas an evaluation of regional therapy variations may be indicated for malignant melanoma, and important biologic as well as therapeutic information obtained, there was little enthusiasm for new studies of variations in local therapy for breast or colorectal cancer.
4. There was a general but not universal opinion that existing cooperative trial mechanisms would be preferable to the initiation of new surgically oriented cooperative groups. A possible exception might be the planning of studies for malignant melanoma.
5. Increased attention to various biologic evaluations in ongoing and future trials involving surgical therapy (particularly receptors, immunologic assessment and recently observed pathologic criteria) is needed.
6. The focus of most broad planning for future surgical oncology research should probably not be on "the operation," but should probably emphasize both screening and management of precancerous processes, biologic concepts relating to the individual cancers now treated by surgeons (with emphasis on distant treatment failure), and the surgical approach to metastatic disease.

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. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFP N01-CB-23915-42

Title: *Use of multiple markers in lung cancer diagnosis*

Deadline: *May 18*

NCI is seeking organizations with the technical capability and interest to perform two or more assays (other than CEA) for circulating (serum) markers associated with human lung cancers. Responders will be provided access to coded serum specimens from a clinical population with small cell and non-small lung carcinoma as well as patients with nonmalignant pulmonary diseases and appropriate healthy controls.

The objective of this study will be to perform a battery of marker measurements on aliquots of blood from the same patients and to determine by appropriate statistical techniques if a combination of markers providing a profile of abnormal change might increase the sensitivity and specificity of the tests.

Potential offerors must have the following: (1) experience and demonstrated proficiency in performing the proposed assays, (2) data for each assay proposed to justify its inclusion in a lung cancer marker panel on patients with various types of lung cancers, both early and late stages; on patients with benign lung diseases and on healthy age and sex-matched controls; (3) adequate laboratory space and facilities for storage of frozen serum samples at -70°C and for performance of assays, and (4) computer facilities and biostatistical staff to evaluate data jointly with the NCI staff after decoding.

A two year contract is anticipated.

Contract Specialist: Rhonda White
RCB, Blair Bldg. Rm 332
301-427-8877

RFP N01-CM-25615-68

Title: *Clinical Data Management*

Deadline: *May 10*

The Clinical Oncology Program, Div. of Cancer Treatment, NCI, is seeking an organization qualified to provide computerized data management support for its Clinical Research Program. The workscope includes completing the development of a data base management system, abstraction of data from official medical records, operating a data coordinating center for simultaneous prospective clinical trials and development and maintenance of new data bases. All work must be performed on the NIH campus in Bethesda, Md.

It is anticipated that one award will be made as a result of this RFP and that an incrementally funded contract will be awarded for a period of 38 months (Sept. 1, 1982 through Oct. 31, 1985). The RFP represents a recompetition of the project, "Clinical Data Retrieval Services." This procurement is set aside 100 percent for small business with a size standard of 500 employees or less.

Contract Specialist: Karlene Wakefield
RCB, Blair Bldg. Rm 212A
301-427-8737

RFP N01-CM-25614-58

Title: *Production and isolation of human macrophage activating factor*

Deadline: *May 7*

The Biological Response Modifiers Program of the Div. of Cancer Treatment, NCI, intends to acquire a large supply of human macrophage activating factor for testing in several in vitro and in vivo systems. The BRMP seeks a contractor who can establish a highly efficient, cost effective procedure for the production and purification of human macrophage activating factor.

The production and purification procedures should be scaled up to ensure the delivery of 1 billion units of human MAF with a specific activity of at least 10^4-10^5 units per mg of protein based on in vitro macrophage mediated specific cytotoxicity against target melanoma tumor cells compared with normal nontumorigenic control cells.

NCI expects delivery of 10 million units of human MAF within six months after award of the contract for the purpose of independent testing and evaluation, with the remaining MAF units to be delivered by 12 months. Experimentally, the production of MAF may involve two major procedures. Offerors may propose to produce and purify human MAF from human peripheral blood lymphocytes or human cell lines grown in tissue culture. Alternatively, they may produce human MAF utilizing bacteria containing genes coding for human MAF arising from recombinant DNA cloning technology.

Contract Specialist: Mary Armstead
RCB, Blair Bldg. Rm 212A
301-427-8737

RFP AMENDMENT

RFP No. NCI-CP-FS-11030-63 entitled, "Support services for a study of cancer following 131-I therapy for hyperthyroidism": The date for receipt of proposals has been extended indefinitely.

The Cancer Letter _Editor Jerry D. Boyd

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