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MSK WITHDRAWS FROM BREAST CANCER NUTRITION STUDY OVER CHEMOTHERAPY ISSUE; PROGRAM STILL "GOING WELL"

The NCI supported nutrition adjuvant study for women with stage 2 breast cancer, controversial from inception and faced with enough problems related to dietary compliance and monitoring, has been

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In Brief

ROBERT DAY NEW AACI PRESIDENT, JOHN POTTER PRESIDENT ELECT; HOWARD APPOINTMENT NEAR

ROBERT DAY, director of the Fred Hutchinson Cancer Research Center, is the new president of the Assn. of American Cancer Institutes, effective at the end of the association's annual meeting this week in Washington. He replaces John Ultmann, director of the Univ. of Chicago Cancer Center. **John Potter,** director of the Vincent Lombardi Cancer Research Center at Georgetown Univ., was elected vice president and president elect. Two new members of the AACI Board of Directors are Paul Carbone, director of the Wisconsin Clinical Cancer Center, and Ross McIntyre, director of the Norris Cotton Cancer Center, the latter two replacing retiring Board members Potter and John Laszlo, Duke Univ.... **JACK WHITE,** who announced last July on his 63rd birthday that he was retiring as director of the Howard Univ. Cancer Center, said Monday that a field of 18 candidates to succeed him had been narrowed to "three excellent people." White said he would remain at the center in another capacity "if (the new director) allows me to".... **FIRST ONCOLOGY** Nursing Society Writing Awards, sponsored by Adria Labs, went to Joyce Yasko and Arlene Fleck for their article in the "Oncology Nursing Forum" entitled, "Prospective Payment: What Will Be the Impact on Cancer Care," and to Patricia Larson for her paper, "Important Behaviors Perceived by Patients with Cancer".... **ROSE KUSHNER'S** article last year in "Ca—A Journal for Clinicians," "Is Aggressive Adjuvant Chemotherapy the Halsted Radical of the 80s?" won her a prize from the Mid-Atlantic chapter of the American Medical Writer's Assn.... **U.S. DISTRICT** Court in D.C. ruled against the "Washington Post" in its suit to force NCI to release information on financial interests of NCI advisory committee members. The court said that information, which advisors are required to submit when appointed, is exempt from Freedom of Information Act provisions.... **FUTURE ANNUAL** meetings of the American Assn. for Cancer Research and American Society of Clinical Oncology will be held in Los Angeles, 1986; Atlanta, 1987; New Orleans, 1988; and San Francisco, 1989. The Oncology Nursing Society will go elsewhere in 1987 and 1988, staying with its policy to avoid states which did not ratify the Equal Rights Amendment, but will join the others in L.A. and San Francisco.

POSTMENOPAUSAL CHEMOTHERAPY DIVIDES CLINICIANS; MILAN DATA INCONCLUSIVE

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involved in another battle over the issue of whether participants in the study should receive adjuvant chemotherapy.

The Div. of Cancer Prevention & Control, its Board of Scientific Counselors, and the nutrition study's steering committee and advisory committee all agreed, after extensive discussion, that chemotherapy would pose too much of a threat to protocol compliance and interpretation of results. They determined that the study be limited to post menopausal patients, since adjuvant chemotherapy has been demonstrated effective in premenopausal patients but not so conclusively in postmenopausal. Withholding chemotherapy from premenopausal stage 2 breast cancer patients could be considered unethical.

There are those who believe it is also unethical, or at least not a good idea, to withhold adjuvant chemotherapy from postmenopausal patients as well. One cancer center which had planned to participate in the study has withdrawn.

DCPC awarded cooperative agreements to the Univ. of Minnesota for the study's nutrition coordinating unit and to eight clinical units, which will accrue the patients and enter them into the program. One of the eight is the American Health Foundation, whose president, Ernst Wynder, conceived the study and convinced NCI it should be carried out. Wynder contends that epidemiology studies in Japan and elsewhere show that low fat diets not only help reduce the incidence of breast cancer but also reduce substantially the risk of recurrence in women who get breast cancer. Wynder, in fact, believes this study will demonstrate that low fat diet can be more effective than chemotherapy in preventing recurrence.

The issue of adjuvant chemotherapy for post-menopausal patients has divided the clinical oncology camp. Both sides can point to studies which show that it is or is not effective, or more likely, that the results are inconclusive. The question will get a thorough airing Sept. 9-11, when NIH will hold a consensus conference on adjuvant chemtherapy for postmenopausal stage 2 breast cancer.

Meanwhile, the DCPC study is going ahead, albeit without Memorial Sloan-Kettering's participation. MSK had agreed to work with American Health Foundation on entering patients in the study. That fell through when the decision was made to leave out chemotherapy.

David Kinne, chief of MSK's Breast Service, wrote Wynder notifying him of the withdrawal. "This represents a significant change from the original proposal," Kinne wrote. "In that proposal, some standard regimen of chemotherapy (such as CMF) would have been administered to one group and the same treatment plus low fat diet to the other. As we discussed at the breast conference you attended, we were concerned that tamoxifen was being omitted, but understood the rationale.

"Now the study has been changed to offer no therapy to one group and diet only to another. This design is unacceptable to all members of our (MSK's) task force. Firstly, adjuvant chemotherapy in our postmenopausal patients seems effective, with disease free survival identical to premenopausal patients. Secondly, if the low fat diet is effective through hormonal mechanisms, we would suggest tamoxifen is easier to administer and monitor than diet. Thirdly, we believe it shows questionable medical judgment to advise no therapy at all to a control group of women with stage 2 breast cancer."

Wynder told **The Cancer Letter** that he is negotiating with another institution in New York to take MSK's place, and that those negotiations may be completed this week.

"If we do give treatment, we will never know what nutrition alone can do," Wynder said.

DCPC Director Peter Greenwald said that so far, MSK is the only study participant to withdraw. Overall, "the study is going well," Greenwald said. The clinical units are just starting to enter patients in the pilot study, in which 40 will be placed on the protocol to work out methods. If there are no hitches, 250 patients then will be entered in the feasibility study required by the DCPC Board and the National Cancer Advisory Board before the project goes to full implementation.

Greenwald said the pilot study evaluation should be available in late August or early September. With results of the consensus conference also due by mid-September, the steering and advisory committees will consider the protocol again.

The investigator who first startled the world with the positive results from adjuvant CMF therapy, and who has contended that the comparatively poor results for postmenopausal patients was due to dose reductions, is now being cited as the authority for not giving postmenopausal adjuvant chemotherapy.

Gianni Bonadonna summarized at last month's annual meeting of the American Society of Clinical Oncology 10 year results from the landmark studies carried out by the Milan group.

The first Milan adjuvant trial randomized 386 women with positive nodes to receive no further treatment after Halsted radical mastectomy or 12 monthly cycles of CMF. The overall 10 year results, Bonadonna reported last month, "indicate that there

remains a significant relapse free survival difference (control group 31.4%, CMF group 43.4%, P<0.001) and a total survival trend (control group 47.3%, CMF group 55.2%) in favor of chemotherapy treated patients.

For premenopausal patients, "its impact remained evident and significant both for relapse free survival (control group 31.4%, CMF group 48.3%, P=0.0005) as well as for total survival (control group 44.8%, CMF group 59%, P<0.02)... Treatment benefit was always inversely related to the number of histologically involved axillary nodes. Best results were observed in the subset with only one to three positive nodes while women with more than 10 positive nodes exhibited poor prognosis. Women who received constant full or near full dose levels of all three drugs exhibited superior 10 year results compared to women who received sub-optimal treatment intensity.

"Salvage therapy applied at first treatment failure failed to produce in the control group superior results compared to the CMF group. Thus, the comparative median survival from first relapse was superimposable between control (37 months) and CMF (32 months) treated groups."

The group's second adjuvant study randomized 459 women locally treated with Halsted or modified radical mastectomy to receive 12 or six monthly cycles of CMF. At eight years, there was no statistically significant difference in relapse free and total survival rates between the two treatment groups. "This finding occurred in both menopausal and nodal subsets," Bonadonna said. "The almost constant trend favoring patients given six cycles vs. those given 12 cycles may be, in part, attributed to the comparatively higher dose levels administered in women treated with six cycles. The results of this study indicate that the maximum cell kill of drug sensitive cells occurs during initial chemotherapy cycles. Thus adjuvant treatment shorter than 12 monthly cycles can spare the patient a considerable amount of toxicity."

The group's third adjuvant study included 140 postmenopausal women age 65 or less. Following modified radicals, patients were treated with six cycles of CMF plus prednisone followed by four cycles of adriamycin and vincristine. In about 90 per cent, chemotherapy was constantly given at 100 per cent of the planned dose. "This was achieved by delaying course in the presence of moderate leukocyte and/or platelet fall rather than reducing temporarily the dose levels, as done in the previous studies," Bonadonna said. "In the six year results, we noticed a relapse free survival (75.2%) and total survival (84.2%) superiority compared to the results previously achieved with CMF in the same menopausal group. The observed superiority of sequential chemotherapy was not documented in women with more than three positive nodes. The observed improvement over CMF in the one to three nodal subset could be attributed either to the frequent administration of full dose regimen or to the effect of AV chemotherapy on a cell subline resistant to CMF, or to both events."

Bonadonna noted that all side effects from any of the regimens were reversible and no patient required admission because of severe toxicity. There were no fatalities attributable to chemotherapy in all 1,326 patients. Pronounced vomiting occurred "almost only after the administration of full dose adriamycin." Severe myelosuppression from CMF was less than eight per cent, with no differences seen among the age groups. "There was no increased incidence of second tumors in the various treatment groups compared to the control group. In particular, no patients with acute leukemia were seen." Hair loss requiring temporary use of a wig was about five per cent from CMF, 10 per cent from CMFP, and 70 per cent from adriamycin.

In his conclusion, Bonadonna admitted there are still plenty of questions to be answered, particularly in relation to menopausal status. "The research findings included in this report are difficult to summarize in terms of clear cut indications as how to apply systemic adjuvant therapy in current medical practice. Considered as a whole, the results of our adjuvant trials indicate that CMF based combinations exerted a prolonged therapeutic activity against a fraction of high risk patients bearing micrometastatic breast cancer at the expense of moderate acute toxicity. Although the consistency in patient selection was reflected in a surprisingly high therapeutic consistency across the various trials, the benefit from adjuvant chemotherapy, as given, was not always of the same magnitude when patient subsets were taken into consideration (e.g. very extensive axillary adenopathy, intensity of drug treatment).

"The puzzle of adjuvant results related to menopausal status is not resolved by current findings. At present, there are no firm indications as far as optimal duration of adjuvant therapy is concerned. From the practical point of view, the results of our trials would suggest that six CMF cycles at full dose could be safely utilized regardless of menopausal, nodal (one to three, four to 10) and receptor status. Alternatively, postmenopausal women with limited nodal extent can receive six cycles of CMFP followed by four cycles of adriamycin, with or without vincristine. In women having greater than 10 positive nodes, adjuvant chemotherapy remains today experimental. The same conclusion applies to women with histologically negative axillary nodes."

HOUSE PASSES WAXMAN BILL, HATCH INTRODUCES HIS; CANCER ACT "WHOLE"

The House of Representatives Monday passed unanimously the Waxman bill reauthorizing federal biomedical research, including the National Cancer Act. At the same time, Sen. Orrin Hatch (R.-Utah) introduced his companion bill which he said is similar enough to the Houser measure that resolving any differences should not be difficult.

The House bill, authored by Henry Waxman (D.-Calif.), chairman of the Health Subcommittee of the Energy & Commerce Committee, is almost identical to the legislation passed by Congress last year but pocket vetoed by President Reagan. Changes made from the 1984 measure included provisions restoring all the special authorities conferred on NCI by the National Cancer Act of 1971 which had been left out inadvertently.

The Waxman bill, in fact, contains everything that NCI and the Assn. of American Cancer Institutes had asked except for a few minor technical matters, AACI members were told this week while holding their annual meeting in Washington. And those technical matters were included in the bill introduced by Hatch.

The Hatch-Waxman legislation, when it emerges from Congress, "will make the National Cancer Act whole again," one observer said.

The two bills continue NCI's bypass budget authority; the President's Cancer Panel; presidential appointment of National Cancer Advisory Board members and the NCI director; cancer control authority; authority of the director to award cancer center core grants and construction grants; and NCI's authority to review contracts and grants and to appoint members of its review committees.

Among improvements long sought by NCI and cancer program advocates which are included in both bills is the authority to award cancer center core grants for up to five years (the limit included in the 1971 Act was three). Also, the NCI director's authority to award grants without concurrence of the NCAB, limited previously to those not exceeding $35,000 in direct costs, would be expanded to include grants up to $50,000.

The House passed the Waxman bill under the procedure known as "suspension of rules," which requires unanimous approval. There were no objections.

The President vetoed the bill last year primarily because it created at NIH a new National Institute for Arthritis, Musculoskeletal & Skin Diseases and a National Institute for Nursing Research. Both of those are in the new Waxman bill, but the Hatch measure does not include the nursing institute.

Last year's pocket veto (made after Congress had adjourned) did not give Congress a chance to override. Waxman and Hatch are determined that that will not happen again, and that if the President does veto it this year, he will be faced with an override vote.

Hatch, speaking at the AACI dinner Monday night, said "There is a new odd couple on Capitol Hill—Henry Waxman and Orrin Hatch." Recalling that he came to the Senate in 1977 as a dyed in the wool conservative, Hatch said "You have to go far to the left to get left of Henry. You don't have to go so far to the right to be right of me, although I'm still a conservative and proud of it."

When the Republicans took control of the Senate in 1980 and Hatch became chairman of the Labor & Human Resources (which includes most health authorizing measures), "Henry Waxman thought he had been sentenced to hell, to have to deal with a conservative chairman." However, "I've learned to admire Henry. He's a brilliant young man. . . I'm proud of Henry Waxman and I'm proud of Ted Kennedy (who Hatch succeeded as head of Senate health forces). We work well together. I think we've done a pretty good job on NIH reauthorization."

Hatch said that if he could have his way completely on the bill, "I would make it less bureaucratic. But I'm not dictatorial. I just try to be sometimes. Henry Waxman is a better dictator than I am," he cracked.

Earlier in the day, AACI members approved a resolution praising Hatch for his support of the cancer program and also praising the work of Hatch's senior aide on health issues, David Sundwall. When the resolution was read to him, Hatch agreed that "you couldn't pay tribute to anyone better than Dave Sundwall."

BYRD PERMITS NCI TO REALLOCATE WVU MONEY, BUT WILL BE BACK IN FY 1986

The question of whether NCI will get to reallocate the $4.5 million Sen. Robert Byrd added to the appropriations bill last year for a cancer center at West Virginia Univ. has been resolved—it will. The money will be awarded for other construction grants approved with high priorities by NCI reviewers and by the National Cancer Advisory Board.

When the NCAB disapproved WVU's application, overturning the initial reviewers' decision to approve it but with a very poor priority score, NCI had hoped the money could go to the hard pressed construction grant fund. Byrd, the Senate minority leader, was not pleased by that decision and had indicated he might insist that the money be returned to the Treasurey if not spent for the designated purpose.

Last week, Byrd inserted in the Appropriations Committee report on the 1985 supplemental

appropriations bill the following statement which ended that prospect:

"The committee continues to be concerned over the lack of a state of the art cancer education, research and treatment resources center in Appalachia. Therefore, the National Cancer Institute is directed to assess the needs of this geographic area and submit a report to this committee no later than Sept. 1, 1985."

That report most certainly will agree that the need exists, and Byrd probably will follow by writing into the FY 1986 appropriations bill an amount for the WVU cancer center. It would be a direct appropriation to the university, bypassing peer review.

By pushing the issue into the next fiscal year, Byrd thus leaves the 1985 appropriations in place.

DCT BOARD APPROVES RECOMPETITIONS FOR DTP, CTEP, BRMP CONTRACTS

Remaining contract recompetition concepts proposed by the Developmental Therapeutics Program of NCI's Div. of Cancer Treatment follow (the other recompetition proposals were published last week in **The Cancer Letter**, along with concepts proposed by the Radiation Research Program). All were approved by the DCT Board of Scientific Counselors.

Also below are the contract recompetition concepts submitted by the Cancer Therapy Evaluation Program and the Biological Response Modifiers Program, as approved by the DCT Board.

Developmental Therapeutics Program Contract Recompetitions

Establishment and monitoring of micro-organisms in isolator maintained foundation colonies. One five year award, estimated annual cost, $60,000. Present contractor is Charles River Breeding Laboratories.

DCT has a large contract program to produce many different strains of mice. These mice are raised principally for use in the various DCT preclinical in vivo screens. If available, animals are also provided at cost to intramural scientists within NIH as well as to grantees. As a result this program is only partially funded by DCT, with cost sharing from the NIH intramural laboratories and grantees. This contract provides quality control for the animals raised at the primary genetic centers.

This contract receives 27 isolator samples weekly from one of our primary genetic centers. These animals or swabs are monitored for bacterial contamination as well as viral contamination. This contract serves as the tool for monthly monitoring of all of our contractors which raise animals in isolators.

It is our intent to renew this effort effective Sept. 1, 1986, by awarding one contract. This will enable us to continually monitor our contract maintained isolators which house our foundation colonies.

Development and production of pharmaceutical dosage forms. One three year award, estimated annual cost $365,000. Present contractor is Univ. of Iowa College of Pharmacy.

The primary objective of this contract is to develop pharmaceutically acceptable dosage forms of new agents assigned by NCI and to manufacture these formulations in batch sizes adequate for phase 1 and/or phase 2 clinical trials. A contract with this work scope has been operational since 1972 and with the Univ. of Iowa since 1974. Most of the formulations are sterile freeze dried dosage forms, but other products have been developed and manufactured including sterile large and small volume injectables, tablets, capsules and a vaginal gel. The ability to have a contract resource to develop and produce a wide variety of pharmaceutical dosage forms has been very useful in meeting the changing needs of NCI's drug development effort.

During the past 20 months of the current contract the Univ. of Iowa has completed development work on 10 compounds including flavone-8-acetic acid, deoxyspergualin, aphidicolin glycinate, HMBA, folic acid 5 mg, anthrapyrazole, and pyrazole. Development of an ipomeanol formulation is nearing completion. Most products were sterile freeze dried dosage forms but small (pyrazole) and large (HMBA) volume liquid products were developed. In addition a 5 mg folic acid tablet and matching placebo were manufactured for use in NCI's chemoprevention program. Also, nearly all the development projects have been subsequently manufactured on production scale. Ipomeanol and pyrazole will be manufactured during the current contract year.

These accomplishments are indicative of the thoroughness of the development work and versatility of the contractor in developing and manufacturing a variety of pharmaceutical dosage forms.

The objectives of the project will be similar to those of the current contract. The contractor will be assigned about four to six dosage form development projects annually. Most of these compounds will not have been formulated previously. However, they will not present significant solubility or stability problems. The contractor will carry out basic preformulation studies: solubility determinations in several parenteral solvents, and stability vs. pH profiles. This information will be used to design a soluble, stable dosage form. Then the stability of this product is evaluated under simulated use conditions including studies at several concentrations, temperatures and in a number of infusion fluids.

The contractor is also required to manufacture these dosage forms in batch sizes adequate for phase 1 clinical trials. Most dosage forms will be sterile freeze dried products. However, the contractor will be required to have the capability to prepare other dosage forms including sterile large and small volume parenterals, tablets and capsules, etc. These products will be used in preclinical toxicology assessments and early pase 1/2 clinical trials.

Development of dosage forms and delivery systems for new antitumor agents. Multiple

awards probably will be made for three years each at an estimated total annual cost of $450,000. Present contractors are Univ. of Kansas, Univ. of Kentucky and Univ. of Arizona.

New compounds are frequently encountered that do not intrinsically possess adequate solubility and stability for intravenous injection. For several years the program has supported a contract effort to specifically resolve difficulties presented by these compounds. Due to the complexity of these problems, the studies are of longer duration than routine formulation development projects. Approaches to significantly improve drug solubility are limited and new methods are clearly needed. We have always asked the responders to the RFP entitled, "Development of Parenteral Drugs for Clinical Investigation" to describe their new approaches to improve drug solubility and stability. Since the response to this particular request was minimal, an RFP entitled, "Novel Drug Formulation and Delivery Systems" was issued but subsequently canceled due to unavailability of funds. There was considerable interest expressed on the part of the research community prior to the cancelation. Therefore, an attempt will be made to incorporate some of the features of both RFPs to provide both the solid formulation research group as well as a group with less depth of experience but a promising new research approach. The title of the initiative has thus been changed.

CONCEPT REVIEW FIGURES ARE ESTIMATES ONLY: RFPs, RFAs NOT YET AVAILABLE

The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

For the past 20 months, this contract effort has been funded at a total of eight staff years divided among three contracts--four at Kansas, two at Kentucky, and two at Arizona. Each contractor is assigned difficult formulations problems. Each project successfully concludes with the contractor providing a small pilot scale batch for evaluation in the tumor screen vs. the bulk drug and an independent analytical assessment. If the material is acceptable by both biological and chemical tests, the compound is then transferred to a contractor with production capability for manufacture of the dosage form for clinical trial. During the past 20 months of the present contract, several projects have been completed and forwarded to another lab for dosage form manufacture: Azacytosine arabinoside, NSC 329680, sulfamic acid derivative; merbarone, triazine antifol, and tetrocarcin. Several compounds have been successfully formulated but dropped from development for other reasons: phyllanthoside, macbecin and tetrocarcin. These contractors have demonstrated the capability to apply existing approaches--solvents, other salts, complexation, surfactants, prodrugs and emulsions to resolve formulation problems, thus permitting their subsequent manufacture and evaluation in toxicology and clinical trials.

The objective of the new project will be an amalgam of the current contract and portions of the novel drug delivery project. A minimum requirement for analytical equipment will be deleted. Greater emphasis will be given to the research approach. However, the target of a useful, soluble, stable formulation will remain.

"Some very promising drugs have been lost to clinical testing because they don't get formulated," DCT Director Bruce Chabner said.

Board member Alan Rosenthal asked if bioavailability data are obtained before the drug goes to clinical testing. "We're close to the point now where we will have that on all compounds," DTP Director Michael Boyd said. "We haven't always in the past because of the number of compounds in the system, and because of other mechanical problems."

"The most effective and rapid synthesis of an agent may not be the most cost efficient," Rosenthal added.

Storage and distribution of clinical drugs. One five year award, estimated first year cost $380,000. Present contractor is Flow Laboratories Inc.

In 1976 a decision was made to contract out the clinical drug storage and shipping functions that were being performed in house by staff of the Pharmaceutical Resources Branch. The increasing demands for this service had outstripped the resources within the program because the number of daily shipments had doubled in the previous two years. The RFP was issued in 1976 and Flow Laboratories was the successful responder. Flow assumed the responsibilities for the storage and distribution of the clinical drugs in September, 1976, and was re-awarded the contract on recompetition in 1981.

The clinical drug storage and distribution operation has successfully received, stored, shipped, and maintained records on tens of millions of dosage forms and about a hundred thousand individual shipments since 1976. Flow currently processes about 50 shipments each day. All orders are processed the same day the order is received from the Investigational Drug Branch. Flow personnel have been available on numerous occasions at night and on weekends for processing of emergency shipments. Frequent inventories have repeatedly shown an extraordinarily low occurrence of discrepancies earning the praise of a GAO auditor. The computer processing of clinical drug request forms and delivery of routine reports has functioned smoothly, including the Drug Enforcement Administration required computer reports for the schedule 1 drug

THC. Additionally, creation of new files and programs, modifications to existing files, as well as numerous special queries have been performed satisfactorily.

The current drug storage and distribution contractor conforms to all applicable regulations, including those of FDA, DEA, OSHA and EPA. The contractor has been extremely responsive to the needs of the program, including cost containment, and the performance has been exemplary.

An RFP will be issued during FY 1986. This contract will involve the use of contract facilities and capabilities to provide a resource for the storage and distribution of the clinical drugs for the Div. of Cancer Treatment. This contract is considered essential to meet the program's needs for efficient and expedient clinical drug delivery to investigators throughout the world. The work scope will involve the receiving of all clinical drug items, proper storage of these items, the packaging and distribution of them to authorized clinical investigators, and the creation and maintenance of adequate computerized records of all transactions. In addition, the capability to arrange for special packaging and labeling of drug products, and the blinding of drugs and distribution for double blind studies will be available. The drug storage area will provide controlled conditions to facilitate optimal storage of all formulated products. In addition, a DEA licensed, highly secure storage facility for scheduled substances providing an adequate amount of refrigerated space will be necessary. The contractor will ship formulated products domestically and to many countries throughout the world. Additionally, adequate records (both manual and computerized) will be maintained to meet all of the requirements of NCI, FDA, DEA and EPA. These records will include receiving and distribution, quarantine, expiration, sampling required and a variety of routine and special activity reports as required.

Biological Response Modifiers Program Contract Recompetition

Characterization and analysis of proteinaceous material. One five year award, estimated annual cost, $160,000. Present contractor is the Univ. of Iowa.

This contract provides BRMP with quality control capability for all biologicals being evaluated preclinically and clinically. Suitable qualitative and quantitative methods are provided to evaluate each biologic to ascertain purity, identity and quality of compounds from batch to batch in bulk and pharmaceutical dosage forms prior to evaluation in animal models and humans. Reports of analysis form the basis for deciding upon alternative sources of biologics to be evaluated in the clinic. The data obtained from analysis of various biologics are also used by BRMP in submission of INDs to FDA for clinical trial approval.

This contract provides capabilities to chemically characterize peptides, proteins, glycoproteins, and polysaccharides that may be used experimentally and/or clinically to modify tumor growth. Assay methods are developed to analyze the substance in bulk dosage form and in common pharmaceutical vehicles. Studies include determination of purity under native and denaturing conditions, amino acid composition, molecular weight, isoelectric point, terminal sequence, development of suitable immunological measurement (radioimmune assays, etc.) and suitable biological assays for qualitative and quantitative evaluations. In the past year this contractor has analyzed and characterized several lots of naturally occurring human alpha, beta and gamma interferons for activity and purity, analyzed several natural and recombinant IL-2 preparations, natural B-cell growth factor preparations, purified the tetrapeptide tuftsin from a commercial source by HPLC for preclinical screening, examined a murine tumor necrosis factor preparation for purity, provided near homogeneous material for monoclonal antibody production and determined the purity of a complex polysaccharide, lentinan.

Future characterization and analysis will focus on biologics with potential antitumor activity that will be evaluated preclinically or clinically by BRMP. The contract will continue to provide capability in the analysis of proteins, peptides, glycoproteins, lipoproteins and polysaccharides and serve as a quality control element. The contract will be expected to provide data on purity, identity, composition, solubility and stability. Methods of analysis may include amino acid analysis, end group and partial sequence analysis, isoelectric focusing, gel electrophoresis, HPLC, carbohydrate and lipid composition, molecular weight determination, radioimmune assays and in vitro cell cytotoxicity assays. In some cases the contractor will prepare heteroantisera or monoclonal antibody against a biologic for use in characterization. The level of effort in the recompetition will remain about the same and about 10 compounds will be analyzed annually.

Chabner asked if the program would be interested in testing compounds submitted by outside investigators. Carl Pinske, chief of the Biological Resource Branch who made the presentation, said that "we would definitely be interested in doing that, although this is primarily set up for intramural testing."

Cancer Therapy Evaluation Program Noncompetitive Contract Renewals

NCI-Pan American Health Organization treatment research program. Three years, estimated cost $390,000 a year.

Fifteen major cancer centers and 26 satellite cancer centers in Latin American countries began in 1977 to perform collaborative clinical trials. The goals of this program were to foster clinical investigation and advance clinical trials methodology experience in Latin America. It was recognized that special cancer patient resources existed in Latin America; substantial numbers of newly diagnosed patients with cervix, gastric, and head and neck cancer were available for studies.

These, together with patients with leukemia, lymphoma, breast and pediatric tumors formed the basis for investigations. All of these tumor systems were highly relevant to the situation in the U.S. and data generated were expected to have an impact on many aspects of clinical trials sponsored by DCT. To be successful, it was recognized that considerable time and effort would have to be donated by U.S. investigators (at "sister" institutions).

"Until recently, we have had uneven performance from this contract," CTEP Director Robert Wittes said. "We looked at it carefully. Some changes have been made in the last one to two years, and increased emphasis was placed on multi-institutional studies. There have been substantial improvements, and we decided that, indeed, we did want to go ahead with it."

The group presently has 538 patients on study.

Board member Robert Goodman asked about the number of protocol violations. Michael Friedman, chief of the Clinical Investigations Branch, said it was less than five per cent.

Responding to Board Chairman Samuel Wells' request to compare the group to the other NCI supported cooperative groups, Wittes said, "If you compare it to the best North American cooperative groups, it is not there yet. But overall, compared to all the groups, it is in the range."

"We have agonized with this for the last five to six years," Chabner said. "It is difficult, considering that U.S. investigators are not getting sufficient funds. On the other hand, they have improved and we feel it is important to encourage clinical oncology research in Latin America."

Rosenthal suggested that other agencies might be asked to help fund the program, and Chabner agreed to look into it. "When I first came here," Wittes said, "I thought the State Dept. should pay all of it. I don"t feel that way now. They are contributing."

At the suggestion of Board member Carol Portlock, the new contract period was reduced from five to three years when the Board approved the concept.

Multimodal treatment of primary breast carcinoma. Two year, no cost extension of the contract with Istituto Nazionale Tumori in Milan.

The extension of this contract will permit the Milan group an additional two years of followup for a total contract period of seven years. No additional funds will be required, since costs are less than predicted.

"(Umberto) Veronesi and (Gianni) Bonadonna are doing some of the most influential studies in the world on breast cancer treatment," Wittes said. "This is worth carrying to completion, particularly the negative node studies."

Board member Paul Calabresi asked if it might be useful to delay a decision until after the NIH consensus conference on breast cancer treatment which will be held in September. "It is unlikely anything will be said there about node negative treatment," Chabner said.

"This trial is not duplicated anywhere," Wittes said. "Good node negative trials are scarce."

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NIH-ES-85-13
Title: Support services for rodent carcinogenesis studies
Deadline: Approximately Aug. 5

The National Institute of Environmental Health Sciences is soliciting proposals from offerors having the capability and facilities to support the in-life portions of the studies; the major objective of the contract would be to treat and house experimental animals following estabalished in vivo rodent carcinogenesis models.

Organizations submitting proposals for this project must have at the time of submission of the proposal or be willing to establish offices, equipment, and technical facilities within 30 minutes commuting time of NIEHS in Research Triangle Park, N.C. A three year contract is anticipated.

Contracting Officer: Marcia Soward
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27709

NCI CONTRACT AWARDS

TITLE: Prime contract/protocol toxicology studies
CONTRACTOR: Battelle Memorial Institute, $99,000.

TITLE: Center for Radiological Physics Program
CONTRACTOR: Yale University, $1,034,427.

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