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MAGNUSON MAKES IT CLEAR SENATE WILL ADD SUBSTANTIAL SUMS TO BUDGET, OBJECTS TO TRAINING GRANT PHASEOUT

Sen. Warren Magnuson (D-Wash.) left little doubt that the Senate will substantially increase cancer funds over the Administration's budget request when he heard NCI's presentation to his HEW Appropriations Subcommittee April 15.

"The cancer act gives you authority to make your budget requests directly to the White House," Magnuson said to NCI Director Frank Rauscher. "What did you request?"

Rauscher replied, "$750 million."

"You requested $750 million, yet they recommended to us $600 million. What started out to be a so-called 'war on cancer' is really more like a skirmish," Magnuson said.

The senator also challenged the Administration's attempt to abandon research training grants and limit training support to post doctoral fellowships. "Do you like that pattern?" Magnuson asked, putting

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In Brief

NCI RUSHING TO COMPLETE DEVELOPMENT OF PROGRAM GRANTS SYSTEM BY JUNE 30

NCI IS WORKING feverishly to whip the program grants concept into shape before Palmer Saunders retires June 30. NCI execs feel the system to replace research contracts at academic institutions will be more acceptable to investigators if it has Saunders' blessing. He has long felt the drift to contracts has threatened the cancer program and has been outspoken about it; he is confident that program grants will be an acceptable substitute for contracts . . . **BUDGET PLANNERS** are drawing up requests for fiscal 1976, and NCI probably will ask Office of Management & Budget for the full $830 million that is authorized in the cancer program extension bill Congress is about to pass. OMB won't leave that much in the President's budget, of course . . . **LOUIS WASSERMAN**, distinguished service professor at Mt. Sinai, is the new chairman of the Cancer Treatment Advisory Committee for NCI. He replaces Gertrude Elion, head of experimental therapy at Wellcome Research Lab whose term on the committee has expired . . . **WHITE HOUSE** is still stalling on naming new members to the National Cancer Advisory Board to replace six whose terms have expired. The delay, undoubtedly due to the President's preoccupation with more dire matters, could result in vacancies through the board's June meeting. Jonathan Rhoads, who has served ably and effectively as NCAB's first chairman, is due to be replaced when Nixon gets around to naming a new chairman. Rhoads' term as a member continues into 1978 and he'll stay on as chairman until a new one is selected . . .

MAGNUSON BACKS TRAINING GRANTS, BLASTS HEW FOR LIMITING NCI ON CONSULTANTS

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Rauscher on the spot.

"We're taking a look at it," Rauscher replied.

"Okay, you have some doubts," Magnuson growled. "I don't see how you can have fellowships without offering some institutional support. Fellowships are no good without the institutions."

Rauscher said the White House has assured him that when the absence of training grants becomes deleterious to the cancer program they will be resumed.

Magnuson asked Rauscher why he has not used the authority given him by the cancer act to hire 50 consultants, in view of the position ceiling slapped on NCI by HEW Secretary Weinberger. Rauscher contends the ceiling has severely hampered the cancer program.

"We thought those 50 consultants were not supposed to count against the ceiling. If they are counted, I want to know about it," Magnuson said.

Rauscher admitted that HEW has counted the consultants against the ceiling, with the result that he has hired only 11.

"Who makes that decision?" Magnuson demanded.

Charles Miller, HEW budget officer, "confessed to some confusion" in interpreting the intent of Congress. Translated, that means HEW brass hunted for an ambiguity in the act's language and then used that as a way to prevent Rauscher from exceeding the ceiling by hiring consultants.

"I would like to have a clear indication from Congress on this," Miller said. Magnuson assured him he'll get it.

Magnuson also objected to the $8.5 million reduction in construction funds. "Norris (Cotton, ranking committee Republican) and I and the committee will take another look at that," Magnuson promised.

The House HEW Appropriations Subcommittee plans to wrap up its work on the bill by mid-June. Magnuson feels he's a little ahead of the usual pace, but it appears unlikely that the bill will be pushed through Congress before the start of the new fiscal year July 1.

LARGE BOWEL STUDY EXPANSION HAMPERED BY LACK OF COORDINATION, NCI ADMITS

NCI's Div. of Cancer Treatment (DCT) plans to substantially expand its programs in large bowel cancer, through combined modality studies for regional and local disease to be developed by the Gastrointestinal Tumor Study Group, and in specific new contracts in the advanced disease area.

But NCI executives themselves admit the program is hampered by the fact that it is diffused through two divisions by at least four different funding mechanisms and administrative approaches.

"The major problem faced by NCI (in large bowel cancer treatment studies) is the coordination of all this research to insure maximum efficiency in the studies without unintended overlap," Stephen Carter, associate director for cancer therapy evaluation, said in a presentation to the Cancer Treatment Advisory Committee.

"What is both lacking and needed is an overall strategy guiding all studies so that priorities of funding, regardless of the mechanism, can be established to reach the goal of increased cure rates as rapidly as possible," Carter said.

DCT has developed its own strategy for integrating chemotherapy into a combined modality approach for all major solid tumors, Carter pointed out. This involves testing of new drugs and regimens in the advanced disease population in order to elucidate the optimal cell kill potential of chemotherapy. Then, chemotherapy will be combined with surgery and/or radiotherapy for the treatment of local and regional disease in the effort to increase the cure rate. In line with this strategy the studies for each of the major gastrointestinal cancers will be reviewed, beginning with investigation of chemotherapy in advanced disease and moving to the protocols for local disease that employ surgery and radiotherapy either alone or in combination.

Carter placed development of new drugs to use in the protocols as one of the highest priorities. He said there are 10 drugs now in phase I studies that have possible application to large bowel cancer, and 20-30 others in various stages of development.

"I would like to see 10 new drugs adequately evaluated for large bowel cancer in phase II studies," Carter said.

Despite objections from some committee members that negative results from standard drugs should preclude further tests with them, Carter insisted further studies with at least some of the older drugs using new regimens should be pursued.

Carter described several current studies being funded by DCT and the Div. of Cancer Research Resources & Centers:

– The Mayo Clinic is performing a comparative phase II study of combined 5 - FU + methyl CCNU + vincristine vs 5 - FU + CAC platinum vs ICRF - 159. In a previous study, the combination of methyl CCNU, 5 - FU, and vincristine showed superiority in objective response rate over that of a control arm of 5 - FU alone. Only a small number of patients were treated with the combination, so an extended phase II trial seemed indicated. Eventually it is planned to compare the combination of 5 - FU and methyl CCNU with or without vincristine.

– The NCI in Milan is currently engaged in a controlled study of methyl CCNU + cyclophosphamide compared to methyl CCNU alone in advanced carcinoma of the large bowel and stomach. The University of Leeds has just completed an evaluation of methyl CCNU and is currently planning its next regimen for study.

– The Eastern Cooperative Oncology Group (ECOG) has completed a study screening drugs which had received little prior testing in colon cancer. Five drugs were tested according to the following schema – Streptozotocin, 0.5 gm/m^2 / wk IV; CCNU, 130 mg/m^2 single dose PO; Bleomycin, 20 mg/m^2 2 x wk IV; 6-Thioguanine, 1.0 mg/kg/d PO; and Procarbazine, 100 mg/d x 7 PO. The results revealed a low, but definite, incidence of remission with 6-Thioguanine and CCNU but the other drugs lacked activity. The current ECOG study is evaluating five new regimens in advanced disease; at the time of disease progression, patients are crossed over to three of these regimens and to a new drug (B-2′-deoxythioguanosine).

– The Southwest Oncology Group has a current study (SOG 7302) intended to compare the effectiveness of 5 - FU + methyl CCNU vs 5 - FU alone in the treatment of disseminated large bowel cancer. The 5 - FU will be given weekly without loading course.

A Central Oncology Group protocol is comparing the incidence, quality, and duration of regression, and survival produced in large bowel cancer by 5 - FU given on four different schedules. This study will compare two "toxic" schedules (loading course IV and weekly IV) with a "non-toxic" schedule and an oral schedule.

– M. D. Anderson has recently evaluated a regimen termed FCC (5 - FU, Cytoxan, and CCNU) that has significant activity in colon carcinoma. Currently, the group is investigating Ftorafur at a dosage of 1 gm/m^2/d x 5 IV q 2-3 wks for all patients who have not received 5 - FU.

– The ECOG is about to begin a protocol involving a double-blind comparison of oral 5 - FU vs. placebo following a resection of large bowel cancer having asymptomatic liver metastases (Dukes D). The Duke's D (distant metastases, peritoneal seeding, parietal or adjacent organ invasion) stage of large bowel cancer is found in 30% of all patients presenting with this tumor. Liver metastases, in particular, are found in about 10% of patients and, when present at the time of initial resection, the prognosis is uniformly dismal. This study will attempt to determine whether oral 5 - FU given immediately after the discovery of asymptomatic liver metastases will increase the symptom free interval, the time to overt disease progression, and, ultimately, the survival in this group when compared to placebo.

– The Central Oncology Group is also evaluating 5 - FU in a similar therapeutic situation, but is comparing intraarterial infusion of the drug vs. the standard intravenous usage. The objectives are to compare the effect on response rate and survival produced by sustained systemic chemotherapy with 5 - FU vs. hepatic artery infusion of 5 - FU, followed by sustained systemic 5 - FU in selected patients with large bowel adenocarcinoma.

– The Southeastern Cooperative Study Group is beginning a protocol that will study methotrexate on three schedules in large bowel cancer. The drug will be administered on the following regimens – 60 mg/m^2 IV weekly x 12; 15 mg/m^2 PO q 6 hrs x 4, weekly x 12; and 125 mg/m^2 PO q 6 hrs x 4, weekly x 12; plus Leucovorin 5 mg PO q 6 hrs x 6 beginning 36 hrs after the first dose of methotrexate.

– At Memorial Sloan-Kettering, Krakoff and Golbey are studying a 3-drug regimen called "MFC" – Mitomycin C, 0.06-0. 08 mg/kg; 5 - FU, 7.5-10 mg/kg; Ara-C, 0.8-2 mg/kg – IV 2 x weekly till toxicity, then weekly.

Radiation therapy has been the treatment of choice in regional or locally unresectable disease while the addition of drugs, such as 5 - FU, has been attempted.

In an early controlled study, the Mayo Clinic compared radiotherapy plus 5 - FU against radiotherapy plus placebo in locally unresectable patients whose known malignant disease could be encompassed by a radiation field no larger than 20 x 20 cm. Each patient received 900-1200 rads per 6 day week to a total dose of 3500-4000 rads, with supervoltage equipment. 5 - FU was given in a total dose of 40-50 mg/kg at the onset of radiation. The mean survival was 16.8 months in 33 patients receiving the x-ray alone compared to 22.8 months in 32 patients who also were given the 5 - FU ($P < 0.05$). In addition, the mean duration of symptomatic control was longer in the 5 - FU treated group although both groups had an equal number of patients achieving symptomatic control. A follow-up study supported by the grant mechanism is comparing 5 - FU alone, 100% oxygen inhalation alone, and 5 - FU plus 100% oxygen inhalation as adjuvants to radiation therapy of locally unresectable carcinoma.

The ECOG recently began a study of locally unresectable stomach, pancreatic, rectal, and biliary tract cancer. This study will evaluate the effectiveness of 5 - FU, as both an adjuvant to radiation therapy and as weekly maintenance versus radiation therapy alone for the locally unresectable rectal lesions. Radiotherapy for the rectal lesions will consist of 4000-5000 rads in fractions of 200 rads given five days a week using either 2 parallel opposed fields, 3 fields, or rotation techniques. The field size is not to exceed 20 x 20 cm and the source will be cobalt 60 or a similar high energy form.

The rationale of employing chemotherapy as a surgical adjuvant has evolved significantly over the past 15 years. Current studies, which largely involve 5 - FU, employ chemotherapy administered for a longer period of time in the hope of eradicating the microscopic foci of metastatic disease that remain after surgery. The Veterans Administration Surgical Adjuvant Cancer Chemotherapy Study Group has recently ceased patient entry on a study of the effect of prolonged intermittent chemotherapy on the survival of male patients following resection for large bowel cancer. This study employed 5 - FU in 5-day courses starting 14 days after surgery and repeated at 6-week intervals for 18 months in patients having curative resections with a poor prognosis for cure.

Additionally, the drug was administered to patients with a proven palliative resection (defined as removal of the primary lesion, but with microscopic evidence of residual disease, i.e., cancer at a resection margin or biopsy of tissues not removed in the resection). Although analysis of this study is not complete at this time, it does not appear that 5 - FU significantly increased the survival of patients

In the current study, the VA group will follow the same experimental design but the chemotherapy will be a combination of methyl CCNU + 5 - FU. The drugs will be administered in five-day courses, beginning as soon after surgery as the patient's condition permits (about 10-14 days after operation), and repeated at seven-week intervals for one year.

TRACOR'S PRIME CONTRACT INCLUDES $1 MILLION FOR ADDITIONAL TESTS

One million dollars has been set aside from the $6.6 million in the Tracor Jitco bioassay prime contract for new subcontracts to test additional chemicals not presently involved in the program.

The new contracts will be awarded on a competitive basis, following government regulations for advertising and negotiating. Tracor will handle all the details and negotiations, but the final agreement must be approved by NCI.

New chemicals to be screened for carcinogenity are being considered by an NCI chemical selection committee. No action on the additional contracts will be taken until the committee makes its selections. Tracor's contract runs through June 30, 1975, so the new subcontracts will have to be awarded prior to that date.

Tracor has announced that it is seeking qualified firms as subcontractors in the program. Sources will be needed for inhalation studies, and studies administering dosages via gavage, skin-painting, dosed-water and dosed-feed. Interested labs should send brochures indicating suitability of facilities, related experience and curriculum vitae of key personnel to Tracor Jitco Inc., 1300 E. Gude Dr., Rockville, Md. 20851, Attn. Subcontracts Dept. Tracor's phone is 301-424-1310.

Included in Tracor's prime contract is a commission to undertake a systems management type study on the cost of screening a chemical for carcinogenesis. NCI has estimated that one screening costs from $50,000 to $175,000. The study will define more accurately what the actual costs are, or what they should be.

Nine existing contracts in the bioassay program will be handled by Tracor as subcontracts when they are up for renewal. All will be renegotiated on a sole source basis by Tracor, with NCI approval.

CONTRACT AWARDS

Title: Immunotherapy mechanism of action of immunopotentiators
Contractor: Medical College of Virginia, $89,800

Title: The role of macrophages in the immune response
Contractor: Palo Alto Medical Research Foundation, $116,412

SOLE SOURCE

Proposals are listed here for information purposes only. RFP's are not available.

Title: Natural occurrence of RNA tumor viruses (genomes)
Contractor: The Jackson Laboratory, Bar Harbor, Maine

Title: Study human milk and mammary tumors
Contractor: Institute for Medical Research, Camden, N. J. (continuation)

Title: Performance of mixed leukocyte cultures
Contractor: Hazleton Laboratories (continuation)

Title: Optimizing electrophoretic separation of proteins with hydrogels
Contractor: Polysciences, Inc., Warrington, Pa. (continuation)

Title: Study in the distribution, disposition and metabolism of antineoplastic agents
Contractor: Instituto Di Ricerche Farmacologiche "Mario Negri" (continuation)

Title: Japan-Hawaii cancer study
Contractor: Kuakini Hospital and Home, Honolulu

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