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NCAB OKAYS EFFORT TO RELAX $5 MILLION LIMIT ON CENTER CORE GRANTS IN CANCER ACT RENEWAL

The National Cancer Advisory Board Monday agreed to ask Congress to relax the $5 million limit on center core grants now fixed in the National Cancer Act when the Act comes up for renewal next year.

The Board had been unable to agree on removal of the $5 million limit at its September meeting, although it did go along with the request to Congress to extend the time limit on core grants from three to five years. Both actions had been recommended by the Board subcommittee, headed by Harold Amos, which was asked to develop suggestions for revisions to the Act.

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In Brief

NO END OF THE YEAR HASSLE THIS TIME – NCI FULL APPROPRIATION FOR FY 1977 RELEASED

NCI'S FY 1977 appropriation has been released by the White House, ending any possibility the President will ask for recisions. NCI will get the full $819 million Congress voted for it. This is the earliest in the fiscal year NCI has received its money since the Cancer Act was approved in 1971; the end of the year frantic hassle to distribute funds won't happen this year. . . . VINCENT DEVITA, director of NCI's Div. of Cancer Treatment, received the first Jeffrey Gottlieb Memorial Award from M.D. Anderson. DeVita was honored for developing the four drug regimen, MOPP, treatment of Hodgkin's disease and his leadership in cancer research. Gottlieb, who was chief of MDA's chemotherapy service, died last year from cancer at the age of 35 after pioneering the clinical use of adriamycin and bleomycin. . . . WATARU SUTOW, professor of pediatrics at M.D. Anderson, and Franz Enzinger, head of the Dept. of Soft Tissue Pathology at the Armed Forces Institute of Pathology, shared the 11th annual Health Memorial Award presented by MDA. Sutow was recognized for his work in improving treatment of many childhood cancers, Enzinger for his expertise in helping standardize cancer terminology. . . . ARNOLD FREEMAN has been appointed chief of the Dept. of Pediatrics at Roswell Park. He has been associate chief since 1971, acting chief since last July. . . . GARY FLAMM, assistant director of NCI's Div. of Cancer Cause & Prevention, to the Clearinghouse on Environmental Carcinogens: "The degree of trust among these sectors (represented by Clearinghouse members) is at a minimum. These are highly emotional issues. As we proceed, I hope we will have a better understanding of why we have these problems and emotions. Why is the translation of animal data to man such a problem? We need to address that question". . . . VINCENT BONO, head of the molecular biology & methods development section in the Div. of Cancer Treatment's Laboratory of Medicinal Chemistry & Biology, has been appointed chief of the DCT Investigational Drug Branch.

NCAB TO ASK CONGRESS TO APPLY CORE GRANT LIMIT ONLY TO DIRECT COSTS

(Continued from page 1)

Amos suggested to the Board this time that instead of asking for removal of the $5 million limit, it should seek somewhat the same language as is in the Heart, Lung & Blood Act which permits annual revision of the dollar limit based on government cost of living figures. Amos also recommended that the revision should specify the limit applies only to direct costs–the government has interpreted existing language to include indirect costs (overhead).

Board Chairman Jonathan Rhoads interpreted the recommendation to mean that a percentage for inflation would be added to the $5 million for each year since the Act became operative in 1972 and that the new limit would be applied only to direct costs. "The inflation factor would kick it up from $5 to $7 million, and if the overhead factor is 40% that would add another $2 million," Rhoads said. "The new figure might be close to $10 million."

A motion to accept the subcommittee's recommendation was approved unanimously.

During the discussion, Benno Schmidt, chairman of the President's Cancer Panel, suggested that since removal of the limit could affect the Memorial Sloan-Kettering Comprehensive Cancer Center, both he and Board member Laurance Rockefeller should absent themselves from the room. Rockefeller is chairman of the Sloan-Kettering board, Schmidt vice chairman. Rhoads agreed, and neither Schmidt nor Rockefeller participated further in the discussion nor voted on the motion.

The Board agreed with other subcommittee recommendations for revisions to the Act:

- Add basic research to describe the type of centers which may be eligible for core grants. The Act now mentions only clinical research in that section.
- Include chemicals as items that NCI may distribute at no charge to non-NCI investigators. The Act now limits this to biological agents.
- Increase the number of expert consultants NCI is permitted to hire from 100 to 200 and authorize reimbursement for travel and moving costs to and from their duty stations.

The Board considered two other significant revisions without reaching any conclusions on the recommendations it will make–the question of seeking exemption from review of NCI supported programs by local Health Systems Agencies, and the problem of how to deal with unwarranted interference in anticancer drug development by the Food & Drug Administration.

NIH Director Donald Fredrickson had advised the Board to refrain from seeking exemption for Cancer Program activities, suggesting it was a problem for all of NIH and should be dealt with from that approach.

Panel member R. Lee Clark told the Board that HSA review would add from three to nine months to the process of awarding grants and contracts, "a process already inordinately slow."

Clark agreed that amending the act authorizing HSAs to exclude cancer programs would be preferable to seeking the exclusion through revision of the Cancer Act. But the Cancer Act expires next July 1, while the HSA Act expires Jan. 1, 1978. Failure to obtain exclusion in the Cancer Act could leave the program with no legislative relief at all if Congress does not accept such exclusion in the HSA act.

Schmidt also expressed disagreement with Fredrickson's position, although saying "that was the only position he could take, that since it is an NIH problem, NCI should not go running off on its own. But if we accept that, we might be comforted, but nothing might happen.

"The best chance we will have," Schmidt continued, "is with our own Act. We'll have more sympathy with our position there than anywhere else." Schmidt pointed out that renewal of the Cancer Act in 1974 "sailed right through" with near unanimous support in Congress. He suggested that "we should find out from the committee chairmen (Paul Rogers of the House and Edward Kennedy of the Senate health subcommittees what problems this would cause them, try to sell them on our view."

The Board agreed to the suggestion that Amos' subcommittee should prepare a position paper on the issue and also draw up language for the Act exempting Cancer Program activities for consideration at the Board's January meeting.

Clark suggested that giving NCI authority over phase I and II drug trials "would have a salutory effect" on the problem with FDA. But Schmidt said he would "like to find some way to solve this without NCI becoming a regulatory agency."

Clark said NCI's authority could be limited to research centers, leaving FDA with control over industry sponsored tests.

"I would rather require FDA to accept NCI's recommendations, rather than take over some of FDA's regulatory authority," Schmidt said.

Div. of Cancer Treatment Director Vincent DeVita said he agreed with Schmidt. "I would prefer not to be involved in approving new INDs. Perhaps we could limit our authority to NCI sponsored drugs. But I must say there have been some days when I wished we did have all the authority," DeVita said.

The Board asked Amos to prepare a recommendation for presentation at the January meeting.

The Board agreed with another recommendation by Fredrickson, that the suggested revision making cancer a reportable disease be dropped. Fredrickson had said that this was an activity of the Center for Health Statistics, another HEW agency, and that it could give the NCI director authority he probably could not legally have.

Schmidt suggested that the statute authorizing the Center to collect health statistics should be amended to specifically make cancer a reportable disease, instead of trying to achieve that through the Cancer Act.

Panel member Paul Marks pointed out that "to make this useful is expensive. This should go to the federal agency with the budget to implement it."

NCAB HAS SOME RESERVATIONS ON MOVE TO TAKE $10 MILLION FROM CONSTRUCTION

Some rumbles of dissatisfaction were expressed by National Cancer Advisory Board members over the decision by NCI to "reprogram" (translation: take away) $10 million from the construction program this year.

Former NCI Director Frank Rauscher told the President's Cancer Panel several months ago that he was going to ask the congressional appropriations committees to approve transfer of $10 million from the $16 million budgeted for construction in FY 1977. Rauscher said the money would be used to increase from 30 to 35% the percentage of approved RO1 (traditional) research grants funded. The Panel went along with the proposal.

But when Acting Director Guy Newell mentioned the plan to the Board Monday, three members voiced reservations. Newell told the Board that the $10 million would go into "high priority activities. . . Certainly, some would go into grants."

Board Member Denman Hammond said, "As I recall, the reprogramming was to increase the rate of payment of RO1s and PO1s (program project grants). You say now it will go into high priority areas but they weren't specified. What has higher priority?" Hammond asked.

"Ro1s, PO1s and core grants," Newell replied. He went on to say that "We don't know what the implications will be to us from the Toxic Substances Act. We might have to use some of it for that."

Board members William Powers and Harold Amos were more concerned about the long range implications. "Will this continue in future years?" Powers asked.

"This was presented to us as an emergency measure," Amos said. "Construction is an important part of our program. I think we need to discuss this further."

"If this is a program decision, we should tell people about it so they won't plan on it," Powers said.

"This is not a program decision," Benno Schmidt responded. "It is not the result of any decision, that the Cancer Program has reached the stage where we no longer will support construction. But we can't say what the future holds."

Chairman Jonathan Rhoads said, "I think we can say we probably won't support much construction in 1978. Even with $955 million (the figure for which NCI has asked) that will barely cover inflation. Probably the only meaningful construction support will come into 1979 fiscal year."

Newell pointed out that the $955 million budget included $19 million for construction.

"And that is also subject to reprogramming," Powers commented.

"It could," Schmidt said.

"Construction funds have mobilized considerable local funds and considerable endowments," Powers said. "This is an unnatural restraint."

"The Board has never discussed the philosophy of construction," Amos said. "It's been supported on a hit or miss basis. It is given two or three mentions in the Cancer Act and therefore has a role we should be familiar with. We need a full dress discussion of construction. . . There are new pressures from Congress for emphasis on environmental carcinogenesis. We have to make the point that if we have to take on new roles, we must have additional money."

Rhoads referred the matter of developing a discussion on construction philosophy to the Board's Subcommittee on Centers & Construction, chaired by Hammond, suggesting it be brought to the Board at its January meeting. He also suggested that consideration be given to changing the 75-25 formula, in which NCI provides 75% of eligible construction costs.

NCI has estimated that for every dollar it commits to providing facilities, another dollar of local funds is generated for the Cancer Program. This includes the 25% matching funds plus additional amounts state and local agencies, institutions and private sources make available contingent on the federal government support.

Even with the entire $16 million originally budgeted for construction in FY 1977, NCI could not fund much more than half the total included in applications either already approved or awaiting review.

A total of $3.5 million was approved for funding in FY 1976 but were carried over when the money ran out before it reached them—$800,000 for Howard Univ., $900,000 for Northwestern Univ., and $1.8 million for the Univ. of Rochester.

Newell said those would be paid first, leaving $2.5 million which would all be used to fund construction of biohazard containment facilities. But NCI has on file seven applications for biohazard facilities totaling nearly $11.5 million—MIT, $1.5 million; Michigan Cancer Foundation, $860,000; Farber Cancer Institute, $3.8 million; Roswell Park, $600,000; Cold Spring Harbor, $1.4 million; Cornell Univ. (Ithaca), $339,000; and Ohio State Univ., $3 million.

Most of these applications have not yet been seen by the appropriate review committees. Some will be reviewed in time for presentation to the Board in January, the rest in May.

Construction applications not related to biohazard awaiting review include Jefferson Medical College,

$1.5 million for radiotherapy facilities; Yale Univ., $1.1 million for basic and clinical science; and American Health Foundation, $1.5 million for environmental carcinogenesis.

Finally, there are two large applications which were approved by the review committees in FY 1976 but not recommended for funding then by the Board –Stanford Univ., $8.3 million, and Georgetown Univ., $4.9 million. They will be competing for funds, if any are available, in the current fiscal year.

The reprogramming request has not yet been presented to the congressional committees. Congress will reconvene Jan. 4, but it may be several weeks after that before the committees are reorganized and operating, although as a practical matter, the requests probably would be disposed of by the two chairmen– Sen. Warren Magnuson (D.-Wash.) and Rep. Daniel Flood (D.-Pa.)

PRELIMINARY REPORT TENDS TO CONFIRM OC ASSOCIATION WITH LIVER TUMORS

A survey conducted by the American College of Surgeons Commission on Cancer to look at the association between liver tumors and oral contraceptive use tends to support such an association, at least for benign tumors, although the data are still preliminary.

Gerald Murphy, director of Roswell Park Memorial Institute, reported the preliminary findings this week to the National Cancer Advisory Board. The Board had asked the Commission on Cancer to undertake the survey in its 750 member hospitals with approved cancer programs, after Board member Philippe Shubik had reported on the growing evidence relating liver tumors to oral contraceptives.

"There is reason enough to be concerned," Murphy said. "It is premature to make any conclusion, but there seems to be some relationship. It appears to be a public health problem."

The Commission on Cancer called upon its network of state liaison fellows and field liaison programs to carry out the survey. A letter was sent to each state liaison fellow in late July, 1976, requesting that all hospitals with cancer programs approved by the American College of Surgeons report all primary benign and malignant liver tumors diagnosed in the six-year period 1970-1975 among patients age 15-45 years. Special report forms were completed by each hospital recording diagnosis, presenting symptomatology, treatment provided, history of oral contraceptive use, and other relevant data. Liaison fellows were requested to complete the data collection by Oct. 1, 1976.

The interim paper reports data received and analyzed through Nov. 3. It includes mainly an analysis of the data on females. A more thorough report is in preparation for publication which will explore in more detail various clinical and epidemiological aspects of the material. The American College of Surgeons is in the meantime requesting, through its network, further data on the reported cases, and these data will be included and discussed in later reports.

Three hundred and fifty-six hospitals reported a total of 432 primary malignant and benign liver tumors among both sexes in the six-year period. Of these cases, 149 tumors were found in males: 91.3% (136) were malignant, 8.7% (13) were benign. The remaining 283 tumors were diagnosed in females. Here, a different diagnostic pattern was evident: 55.5% (157) were benign, 44.5% (126) were malignant.

The report included this summary:

"1. The survey of primary liver tumors by the American College of Surgeons was timely, and the response through their field liaison program was surprisingly effective. Through this survey approach, a very large material of primary liver tumors was collected, including a total of 157 benign tumors in females. There is no doubt that there is a potential for the further utilization of the field state officer liaison network.

"2. A substantial difference was observed in the proportion of benign to malignant tumors among oral contraceptive users (74.6%) as compared to non-users (50%). The greater proportion of benign tumors among oral contraceptive users was consistent in all age groups. These results would seem to support the suggested association between oral contraceptive use and benign liver tumors.

"3. Benign liver tumors were diagnosed as well in non-users of oral contraceptives. Among the non-users, the frequency of benign tumors increases with age.

"4. Hepatic cell adenomas and focal nodular hyperplasias were observed more frequently among oral contraceptive users than non-users.

"5. Intraperitoneal bleeding was a presenting symptom in hepatic cell adenoma in only 12% of cases.

"6. The data collected on type of contraceptive used and duration of usage in this survey do not lend themselves to conclusive analysis."

The report drew these implications:

"There are several clinical and epidemiological implications that can be drawn from this survey material, even at this interim stage of analysis. The large number of benign tumors reported does suggest that clinicians should be alert to possible liver pathology in young women on oral contraceptives presenting with even vague and non-specific abdominal symptoms. Consideration should be given to any liver pathology before oral contraceptives are prescribed. Careful followup of oral contraceptive users with a history of liver pathology is indicated.

"From the epidemiological point of view this survey conducted under the auspices of the American College of Surgeons has already stimulated some hospital registrars to include all primary liver tumors in their registries, and it is hoped that this practice

will be adopted by all registrars in hospitals with approved cancer programs.

"Another problem of importance in the epidemiological study of benign liver tumors highlighted by the survey material and recognized by clinicians is the confusion of nomenclature and classification of these neoplasias. The American College of Surgeons intends to pursue these difficulties by obtaining where possible slides of the benign liver tumors in this report and designating a group of pathologists to carry out an independent review of the histologic diagnoses, with a view toward clarifying terminology.

"Considering the widespread use of the oral contraceptive methods in the United States and in fact throughout the world, there is an urgent need for collaborative controlled retrospective studies to quickly ascertain the risk of primary liver tumors in users of oral contraceptives and to study the relevance of such factors as duration and pattern of use of oral contraceptives, age at start of such use, synthetic estrogen taken and previous liver disease."

On the type of contraceptive used, the report said:

"The survey report forms completed by the hospitals included information on type of oral contraceptive used and length of time taken. These data were not always available. . . . Oral contraceptives usually contain a synthetic progestogen and a synthetic estrogen in varying dosages. Various progesogens are prescribed, but only two synthetic estrogens are in use: ethinyl estradiol and mestranol. Mestranol is demethylated in the liver to ethinyl estradiol. Fifty-four tumors occurred in women on the synthetic estrogen mestranol, 18 in women on ethinyl estradiol and 61 in women who did not know the type of oral contraceptives they were taking, or who were on other estrogen therapy. Proportionately more women in the "unknown" group had malignant tumors.

"The finding of far more tumors among mestranol users concurs with the findings in a controlled study by Edmondson and colleagues, who compared 68 women on oral contraceptives, 34 with benign liver tumors and 34 liver-disease-free controls. In Edmondson's material, all the women with benign liver tumors were taking mestranol, while half the control cases were using ethinyl estradiol.

In the present study, analysis of length of usage by synthetic estrogen showed no differences. Analysis of frequency of tumors by progestogen used was also inconclusive.

"However, it should be remembered that the first oral contraceptives on the market contained mestranol exclusively. Ethinyl estradiol was first introduced as an oral contraceptive in 1964, and marketing figures for oral contraceptive prescriptions indicate that until 1970 mestranol was used more frequently than ethinyl estradiol by the general population. Therefore the fact that more women with tumors were observed to be taking mestranol may reflect in very large part the greater availability for a longer period of time of this preparation. The data do merit, however, further controlled study."

Board member Bruce Ames suggested that the number of tumors found were "relatively few" when considering the millions of women using oral contraceptives.

Murphy agreed and said the commission was attempting to get data on number of users but had been unable to do so.

"For this to be meaningful, we have to have the number of cases per million users," Ames insisted.

Benno Schmidt said that should be NCI's job, not the commission's. "We should also take into account Shubik's point, that we should not be lulled into a sense of security by relatively low figures. It may be too early for many taking the pill to have the evidence of tumor manifesting itself."

Working with Murphy on the survey were Josef Vana, Roswell Park; Billie Arnoff, chairman of the field liaison committee, Commission on Cancer, and Harvey Baker, chairman of the Commission.

NCI ENCOURAGES DEVELOPMENT OF NEW REGIONAL MULTIMODAL CLINICAL GROUPS

Now that the reorganization and shaking out of existing Clinical Cooperative Groups has been more or less completed, the Div. of Cancer Treatment is considering supporting a new type of cooperative group. These new groups would be more limited geographically or regionally than the existing groups, designed to work in areas not covered by existing groups.

The new groups will be multimodal from the start, would get patients in all stages of disease, and probably would be identified primarily with single institutions or centers, although members could be located in a variety of settings.

DCT Director Vincent DeVita told representatives of cancer centers at their recent meeting that one or two such groups might be set up this year. He didn't mention any specific ones, but *The Cancer Letter* learned that one might be in Northern California. Stephen Carter, former DCT deputy director, is the director of the Northern California Cancer Program, a multi-institutional organization which Carter hopes to develop into a comprehensive cancer center.

Since the Western Cancer Study Group was phased out, there have been no cooperative group trials in Northern California. Carter's group would attempt to fill that void, with all modalities represented, working out of the affiliated institutions—Stanford, Univ. of California in Berkeley, San Francisco and Davis, Univ. of Nevada (Reno), West Coast Cancer Foundation—and community hospitals and clinics.

DeVita later told the Cancer Clinical Investigation Review Committee that he sees such regional groups as a "vertical cut through the community," with the

hope of involving more private physicians. They should involve all modalities from the outset. "The feeling prevails that the old groups are still chemotherapy groups despite attempts to go multimodal," he said.

CCIRC member Stephen Jones asked if the regional groups could not be better as subsets of a national group. DeVita said that private physicians do not have the time to travel to meetings thousands of miles away.

DeVita said DCT has been receiving inquiries from persons interested in forming the new groups. Only those whose regions and capabilities fit the concepts he described are encouraged to proceed.

CCIRC Chairman Giulio D'Angio noted that it would be "extremely hard to mount a group without a lot of guidance." DeVita responded, "We'll have to take a certain amount on faith. That's a problem with all new groups."

CCIRC member Nell Sedransk asked about more money for statistical analysis, commenting that in the past if not sufficiently funded for that task, the groups simply did less statistical gathering.

"We would be receptive to supporting major expansion in this area," DeVita said.

Member John Bennett, discussing protection of human subjects, said many small institutions have no evaluation committees. DeVita pointed out that if a hospital has no evaluation committee, its staff cannot do clinical research.

DeVita said cooperative groups must establish data safety monitoring boards, a new FDA requirement, and must have periodic protocol review.

DeVita asked the committee to be more definite in assigning priority scores. "If you are ambivalent yourselves, and approve an application but give it a low priority score, it puts us in a bind. I cannot defend funding a low priority." He referred to the GAO report calling attention to low priority research being funded. Members asked what scores they should give. DeVita said that 350 is low, funding rarely goes below 260, and that if they like an application they should give it a score of at least 250.

DeVita outlined accomplishments in the year since the CCIRC and cooperative groups were moved into DCT.

—Responded to the Food & Drug Administration's request for a description of the cooperative group program, which FDA appeared not to understand.

—Began consolidating multiple cooperative groups at single institutions into fewer groups and facilitated changes by members requesting a move.

—Brought the group chairmen into budget decisions. "Group chairmen in the past never knew in advance the amount of funds for their groups," DeVita said.

—Began at attempt to share resources between the contract groups and the cooperative groups.

—Moved "very fast" toward multimodality.

—Assisted in developing a multiple sole source contract for cooperative groups awarded by the Div. of Cancer Control. The aim is to reach community hospitals with the groups.

—Set up a mechanism for members of discontinued groups to go to new groups.

—Catalogued group protocols by disease site.

—Increased membership in the CCIRC, to handle the sizeable load.

DeVita said DCT is following a "critical but generous" policy toward the cooperative groups, and cautioned the review committee that it "ought not approve clinical research unless it is good research."

The generous part included a $5 million increase in funds to groups.

CONTRACT AWARDS

Title: Cancer immunotherapy: Animal models for treatment of minimal residual systemic tumor
Contractor: Pennsylvania State Univ., $175,278.

Title: Rhesus monkey histocompatability studies
Contractor: Litton Bionetics, $223,304.

Title: Genetic control of immune responses in relation to cancer
Contractor: UCLA, $90,881.

Title: Improvement in migration inhibition assay
Contractor: Univ. of Texas Health Science Center (San Antonio), $81,842.

Title: Clinical evaluation of immunodiagnostic tests
Contractor: California State Univ. (Fullerton), $28,435.

Title: Sera collection from high cancer risk populations
Contractor: Philadelphia Geriatric Center, $52,768.

Title: CEA and related tumor associated antigens in cancer diagnosis
Contractor: Health Research Inc., Buffalo, $70,586.

Title: Synthesis and study of potential inhibitors of the utilization of pyrimidines
Contractor: St. Jude's Children's Research Hospital, $183,145.

Title: Molecular hybridization studies with RNA of high specific activity
Contractor: Sloan Kettering, $82,366.

National cancer consultative programs for hospitals

The Cancer Letter—*Editor* JERRY D. BOYD

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