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COOPERATIVE GROUP CHAIRMEN TOLD THEY MUST DO THEIR OWN PLANNING, WILL GET FUNDS INCREASE

NCI's Div. of Cancer Treatment "came through loud and clear" in what it expects from—and is offering to—the clinical cooperative groups now that the groups have been moved to DCT:

* The groups must plan their activities along disease oriented lines, determine what their existing resources are, and present their proposals to NCI with reasonable justification for their additional requirements.
* DCT will provide the additional resources, in the form of substantially increased funding over what the groups have been receiving.

James Holland, chairman of Acute Leukemia Cooperative Group B, told his fellow chairmen when they met last week that the message from DCT Director Vincent DeVita and Deputy Director Stephen Carter "came through loud and clear to me." Holland said he interpreted the remarks of DeVita and Carter as placing the entire resources of DCT behind the cooperative groups, including the shift to the groups of some of the money now going out in contracts.

(Continued to page 2)

In Brief

FRENCH 10 YEARS BEHIND IN TREATMENT TECHNIQUES, RAUSCHER TELLS PREMIER; EUROPEAN INTEREST GROWS

FRANCE IS 10 years behind the U.S. in applying the latest techniques in treating cancer, NCI Director Frank Rauscher told French Premier Giscard d'Estaing recently. France and other European countries are showing increased interest in the U.S. cancer program, and Rauscher's comment to the premier no doubt will stimulate that interest. Rauscher asked cooperative group chairmen last week to accept some of the responsibility for working with other countries, "rather than having NCI quarterback" all such efforts. . . . **NCAB MEETING** Oct. 6-8 will include the annual program review by the Board. Topics will be the treatment program, priorities in environmental carcinogenesis, and cancer control's community "saturation" program. . . . **UPDATE** on current status of radiation therapy in the cure and management of cancer will be presented at the Oct. 9-11 meeting of the American Society of Therapeutic Radiologists in San Francisco. . . . **SEVENTH INTERNATIONAL** Symposium on Comparative Research on Leukemia and Related Diseases will be held Oct. 13-18 in Copenhagen. NCI's Virus Cancer Program and the Leukemia Society of America are primary sponsors of the meeting. Reports will be presented on evolutionary changes and growth regulation in normal and cancerous cells; interactions between the immune system, animal cells and viruses associated with cancer; population studies of leukemia and lymphomas in animals and man; progress in treating leukemia and other cancers of the blood and lymph systems; and new concepts of the role of viruses in human cancers.

GROUP GRANTS WILL BE RAISED TO LEVEL OF CONTRACTS IF NEED CAN BE SHOWN

(Continued from page 1)

"We've said we're capable of doing more than we have been doing," Holland said. "Now we need to substantiate it."

Many cooperative group members feared that DCT with its established clinical trials contract-funded program, once it had administrative control of the groups, would deemphasize the groups, perhaps phase them out altogether.

DeVita and Carter went to considerable effort to dispel those thoughts. Carter amazed, and obviously pleased, the chairmen when he said flatly, "We won't put out an RFP (for clinical treatment trials) without first coming to the cooperative groups and asking if you can do it."

"That's a major statement of policy," one of the chairmen said.

Carter noted that with the groups now within DCT, many of the division's contract jobs can be funded by grants. "We won't put out an RFP without looking at all our resources to determine how best a particular program can be funded. We may find that it can be funded just through an increase in an existing grant."

DeVita commented, "It will be a hell of a lot easier to work through the groups than contracts," considering the manpower shortage at NCI and the manpower required to develop and manage contract programs.

DeVita made it clear that the initiatives, the planning, the suggestions involved in beefing up the groups and in moving from their traditional chemotherapy-advanced disease patient programs to multimodality-early disease emphasis would have to come from the group members themselves. "There is a need for centralized planning," he said. "That smacks of big brother, telling you how to do things. But you must realize that this planning will be done by you, by the people in the field, not by NCI."

DeVita suggested that the group chairmen, meeting at least four times a year, be the entity primarily responsible for developing and organizing the plans. He also suggested that committees be formed for each of five disease categories—GI, lung, breast, genital-urinary and pediatric.

Holland was elected chairman of the group chairmen's committee and of the executive committee, which will exercise all responsibilities of the group chairmen between meetings. Others elected by the chairmen to the executive committee were Paul Carbone, Eastern Cooperative Oncology Group; Bernard Fisher, Primary Breast Cancer Therapy Group; Denman Hammond, Children's Cancer Study Group; Simon Kramer, Radiotherapy Oncology Group; and George Lewis, Gynecological Oncology Group.

Among items covered in the day-long meeting:

- Role of the chairmen's committee. "Vince said it would help if we could give him advance plans on membership changes, plans involving funding, advise on optimal size of groups, geographic location, what if any new groups to develop, possible phasing out of groups," Holland said. "Is there an optimal size?"

"No, that will vary according to what you're trying to do," Fisher said.

Carbone suggested that the disease-oriented committees could make the determination of whether new groups should be formed or old ones dropped, reporting to the chairmen's committee.

Kramer said this could be interpreted as self serving, that the chairmen could be accused of protecting vested interests. "Are we to be judge and jury?"

"Should we or should we not have a voice?" Holland asked. "I recognize there are vested interests. But if we sit here and say all groups should be equally funded, we're useless as an advisory body."

- Disparity in funding between grants and contracts. Lewis cited an example in which a cooperative group lost patients to an institution which was doing the same job under an NCI contract and which was getting more money for approximately the same amount of work. Holland pointed out that trials conducted by the groups cost NCI about $750 per patient, while NCI contractors were paid an average of $2,000 per patient.

Carter commented that the difference may be due largely to the difference in patients. Contractors have been dealing more with early disease and thus need a longer followup time, and they have been using more expensive multimodality therapy.

DeVita insisted there will be equivalency in funding between the groups and DCT contractors. "In the past, groups have been pegged closely to the traditional, unsolicited grants. They ought not to. They ought to be pegged to what we feel is the most interesting thing to do . . . Funding will be equivalent, but narrowed by review to assure the best work possible."

- Coordination. Hammond commented that "there is nothing inherent in the consolidation of NCI therapeutic activities into one division that eliminates lack of coordination . . . the administrative change doesn't do anything in itself. It only gives you the opportunity."

Holland suggested that DCT should have a moratorium on new contract programs. DeVita agreed "in the sense that there won't be any without the knowledge and input of the groups."

- Controls. John Durant, Southeastern Cancer Study Group, asked whether historical controls will be adequate for future cooperative group clinical trials or will concurrent controls always be required.

"I view that as your own problem, to determine as you feel necessary," DeVita responded. "That's something we'll all never agree on. It is a problem for each disease committee to determine."

- Community physician participation in research. Holland commented that physicians engaged in clinic-

al research "have to have some academic connection. The community physician can't undertake it himself, on his own."

DeVita agreed, and referred to an impending response from a community group to a DCT RFP in ovarian cancer, indicating he had serious doubts about how it would be received by NCI.

"Are you referring to ACCC?" Hammond asked, meaning the Assn. of Community Cancer Centers which has said it will submit such a proposal (***The Cancer Letter,*** Sept. 5). DeVita said he was.

Hammond noted that ACCC has a planning grant to determine how the organization can interact with cooperative groups and cancer centers. "They do not intend to go off on their own," Hammond said. "If guided properly, they could be a major resource. They have some good people in the smaller institutions. Perhaps they could tie into existing groups."

DeVita agreed that most of the annual total of 326,000 cancer patients are treated at the community level.

The problem of obtaining patients in sufficient numbers for clinical research has been of growing concern to NCI and the cooperative groups. Competition for patients at the cancer centers has resulted from the growing number of clinical trials and the inability of the centers to attract or care for patients in the required numbers.

Durant suggested that funding of community centers through cancer control programs will result in more patients staying in the community and out of research. "We'll just have to get research done in the community," he said.

Louis Wasserman, Polycythemia Vera Study Group, said the problem is to get the physician to put his patient in a research protocol. "We need to convince the local physicians in the communities to get into research."

Fisher agreed. "We're not reaching out for the patients, but for the physicians. We have to educate them." Fisher said his breast cancer group has had no serious problems in getting enough patients.

"This competition for patients bothers me," DeVita said. "There are many thousands of patients out there who never get into research programs."

• Cancer control and the relationship to the cooperative groups. Following a discussion on the difficulty of separating control from treatment research and the complicating factor that the Div. of Cancer Control & Rehabilitation cannot fund treatment research, Holland suggested that a redefinition of DCCR's role may be needed.

NCI Director Frank Rauscher had earlier commented that "control is the step we take after you fellows show us the best new treatment." Holland responded that "it is rare when what is new isn't also the best."

DeVita again tossed the ball back to the committee, suggesting that it could take on the responsibility of "identifying the cut off," when a new regimen should go into control.

CCIRC LEARNS IT HAS LOST POLICY MAKING, PROTOCOL REVIEW AUTHORITY

Members of the Cancer Clinical Investigation Review Committee learned this week that from now on the committee's role in the cooperative group program will not include policy making or protocol review.

When the cooperative groups were under the administrative control of the Div. of Research Resources & Centers, CCIRC had a dual function as both the review body for grant applications from the groups and the policy maker for the program.

One of the recommendations of the Potomac Conference was that CCIRC be relieved of the policy role. DeVita agreed with that recommendation, and when CCIRC was moved along with the cooperative groups into the Div. of Cancer Treatment, he exercised his authority to implement it.

"CCIRC should remain primarily concerned with the review process (meaning the review of grant applications)," DeVita told committee members Monday. "Group chairmen and ourselves (meaning DCT staff and the division's various advisory bodies, the Board of Scientific Counselors in particular) will make policy. CCIRC should remain aloof and independent and devote its energies to review."

DeVita later told ***The Cancer Letter*** he realized CCIRC "can't be totally removed from policy matters, but review is its major function and it is the only body in the program doing the review."

DeVita also told committee members he was turning over to DCT staff the job of reviewing protocols proposed by group members. "Protocol review has been a sore point," he said. Two reasons for making this change:

* Coordination. "It has never been a consideration in protocol review of what else is being done in that area. That's what we will do."

* Delays in getting protocols approved by CCIRC. "Protocol review has been slow and ineffectual. . . Staff will do the review, at least until the logjam is relieved . . . Part of the problem has been, and I say frankly that this is true of some CCIRC members as well as your outside consultants, that when protocols come in they often sit on desks."

Some committee members took exception to this decision. Montague Lane, Baylor, argued that although "many aspects of protocol review could be carried out by staff, there must be scientific and statistical review. . . Our objections and comments on the science outght to be in the record. . . If a group does not need our advice and they turn out wrong, they ought to pay the price."

DeVita argued that retrospective analysis has never been done and insisted that responsibility for developing a protocol belongs to the group anyway.

"I view with considerable alarm your proposal that it be entirely internal," said Carol Newton, UCLA.

"But it hasn't worked," DeVita responded.

"Then find out why it hasn't worked and improve it," Newton said.

Howard Lessner, Univ. of Miami, disagreed with fellow committee members. "Frankly, I believe protocol review was better when it was done by staff, particularly when Diane Fink was doing it (before Fink became director of the Div. of Cancer Control & Rehabilitation).

When Lane pointed out that Fink used consultants to assist with the review, DeVita said he would urge his staff also to use consultants where appropriate.

"We will use CCIRC to deal with controversial protocols," DeVita said. "But staff will handle most of them."

On another subject, Lane referred to a recent RFP put out by DCT in which the contractor would be required to supply at least 400 patients a year, 25 per disease category. "I don't know of a single institution in the cooperative group program that could contribute 400 patients to a study," Lane said. His objection dealt with DCT's avowed intention of giving the groups first crack at any new division-supported clinical trials.

"That's exactly why we went to contract, because no group had that many patients," DeVita said. "We put this out in an attempt to get some major centers not now doing therapeutic studies."

"Who could? (meet that requirement)" asked Audrey Evans, Philadelphia Children's Hospital.

"We have had three responses, from major institutions not now involved in any existing mechanism," DeVita said.

ANTI-NCI FORCES LOSE BID TO TAKE $70 MILLION FROM CANCER PROGRAM

Pro-cancer program forces reportedly have turned back an attempt to take $70 million from the $825 million approved for NCI by the Senate Appropriations Committee and distribute it among the other institutes at NIH.

Backers of the abortive plan, which may have included some Administration officials, were said to have lined up a small group of senators to support the plan when the HEW appropriations bill reached the Senate floor last week.

They were looking hungrily at the $100 million the Senate committee added onto NCI appropriations for fiscal 1976 over the figure approved by the House. The Senate committee had already added more than $73 million over the House bill to five institutes–Heart & Lung, Dental, Arthritis, Aging and Eye–and the Div. of Research Resources. But the anti-NCI people wanted at least that much more for other institutes.

When the bill reached the floor, the Senate became embroiled in debate over busing and other elements of education and welfare appropriations, giving NCI backers time to go to work. At press time this week, no amendment to take funds from NCI had been introduced. Sources involved in the struggle backing NCI were convinced that the plan had been scrapped.

It could still be months before NIH and NCI funds for the current fiscal year are finalized, even if the Senate approves the bill this week. Conference with the House could take another week at least, the veto threat remains, and the President is expected to submit recision requests even if he signs the bill.

NCI ADVISORY GROUP MEETINGS FOR OCTOBER

Cancer Research Center Review Committee–Oct. 3–4, Linden Hill Hotel, 5400 Pooks Hill Rd., Bethesda, open Oct. 3, 8:30–10 a.m.
Combined Modality Committee and Clinical Trials Committee, Div. of Cancer Treatment–Oct. 3, Bldg 31 Room 6, 9 a.m.–5 p.m., all open.
National Cancer Advisory Board Subcommittee on Centers–Oct. 5, Bldg 31 Room 7, open 7:30 p.m.–9 p.m.
National Cancer Advisory Board–Oct. 6–8, Bldg 31 Room 6; Oct. 6, 9 a.m.–6 p.m., Oct. 7, 9 a.m.–5 p.m., Oct. 8, 9 a.m.–adjournment, all open.
Cancer Control Grant Review Committee–Oct. 6–7, Bldg 31 Room 8, open Oct. 6, 8:30 a.m.–9.
Virus Cancer Program Scientific Review Committee A–Oct. 6, Bldg 37 Room 1B04, open 9–10 a.m.
Virus Cancer Program Scientific Review Committee B–Oct. 7, Bldg 37 Room 1B04, open 9–9:30 a.m.
President's Cancer Panel–Oct. 8, Bldg 31 Room 6, 2:30 p.m., open.
Cancer Special Programs Advisory Committee–Oct. 10–11, Bldg 31 Room 8, open Oct. 10, 9–9:30 a.m.
Workshop and State of the Art Conference on School Health Education Programs as They Relate to Cancer Control–Oct. 12–15, Denver Hilton; Oct. 12, 5–9 p.m.; Oct. 13-15, 9 a.m.–5 p.m., all open.
Board of Scientific Counselors, Div. of Cancer Biology & Diagnosis–Oct. 16–17, Bldg 31 Room 6, open Oct. 16, 9 a.m.–5 p.m.
Conference on "Early Lesions and the Development of Epithelial Cancer"–Oct. 21–23, NIH Bldg 1, Wilson Hall, 8:30 a.m.–5 p.m. each day, all open.
President's Biomedical Research Panel–Oct. 27–28, 2401 E St. N.W., Washington D.C., Suite 3100. Open 9 a.m.–5 p.m. both days.
Cancer Control & Rehabilitation Advisory Committee–Oct. 28, Bldg 31 Room 4, open 9 a.m.–1 p.m.
Virus Cancer Program Advisory Committee–Oct. 30–31, Bldg 31 Room 4, starts 10 a.m. both days, all open.

NO TAKERS YET IN EC CENTERS PROGRAM; SUBCOMMITTEE ASKED FOR DEFINITION

Isn't anyone out there interested in NCI's new specialized centers program in environmental carcinogenesis?

The National Cancer Advisory Board approved the program last June, and provisions were made to accept letters of intent from organizations interested in obtaining planning grants toward development of the new centers (*The Cancer Letter*, July 4). Planning grants will range from $25,000 to $40,000, and the entire program involving the establishment of five to ten new centers will be supported by an estimated $20-30 million by the end of the second year.

So far, however, NCI has yet to receive its first

letter of intent for the planning. Announcement of the new program has caused some confusion, however. The Div. of Research Resources & Centers, which adminsters NCI grants and the centers program, has received unnecessary letters of intent from indidivuals who plan to submit regular grant applications for carcinogenesis studies.

Letters of intent are not required in the traditional grant programs and program projects in carcinogenesis. Established NIH procedures should be followed.

One reason why the new specialized centers program has not generated any apparent interest may be that universities are cool toward it.

Arnold Brown, a member of the NCAB Subcommittee on Environmental Carcinogenesis, said at a recent subcommittee meeting that universities do not necessarily see the advantages of institutionalizing such activities.

Committee Chairman Philippe Shubik said he did not think there would be a problem finding a half dozen or so universities which would enthusiastically support such centers, provided they would get the kind of federal funding that would be necessary to put and keep them in business.

In any case, Shubik and the subcommittee placed the new specialized centers at the top of their priority list of projects needed to generate the interest in and support for environmental carcinogenesis studies called for by the perceived magnitude of the problem—that it is responsible for as much as 80-90% of all cancer. They worked hard to sell the specialized centers to the Board and will be considerably embarrassed if there are no takers.

The subcommittee meanwhile was handed another controversial task by NCI Director Frank Rauscher, to come up with a definition of an environmental carcinogen. Such a definition could have broad implications for the regulatory agencies, such as FDA and the Environmental Protection Agency, particularly if it should result in extending or broadening their regulatory activities.

Umberto Saffiotti, associate director for carcinogenesis in NCI's Div. of Cancer Cause & Prevention, submitted a draft statement as a basis for discussion of what a definition should include. He suggested that an important consideration would be to arrive at an understanding of what policies should be regarding a suspected carcinogen in the absence of good data.

"Policies shouldn't be the same for scanty data versus good data," Saffiotti said. "We should not assume the safety of a substance if we don't have good data, or if we have only scanty data."

James Peters, DCC&P director, agreed. "When we have good data, there is not so much of a problem. It's the gray area in the middle that causes the most trouble, and saddles us with a sore situation as in cyclamates," Peters said.

The subcommittee discussed the prospect of requiring industry to pay for carcinogenesis studies of new substances and the role NCI should play in such studies. NCI now conducts (and pays for) studies on about 300 chemicals a year.

Shubik asked subcommittee member Bernard Weinstein to write a draft definition for consideration at the next meeting.

Saffiotti's draft of "summary statements" as he called them included the following:

- The majority of human cancers are believed to be caused by exposure to extrinsic carcinogenic factors which include physical and chemical agents, many of which are avoidable.
- Chemical carcinogenesis is characterized by a long latency period which in humans can be as long as 30 years or more between the initial exposure and the appearance of symptoms of the disease.
- A chemical carcinogen is any substance which has been shown to cause tumors in adequately conducted studies in man or in animals. A critical evaluation of the relevant studies, both qualitative and quantitative, is needed in order to establish this causal relationship, which may be evidenced by significantly increased incidences of tumors and or by shortening the latency period between the exposure and the development of tumors.
- Any substance which has been shown to cause tumors in any mammalian species in adequately conducted studies at any dose level must be considered a carcinogenic hazard to humans, unless proven otherwise.
- Chemical carcinogenesis appears to be a specific biological process, induced by chemicals which can undergo certain chemical reactions with cellular target macromolecules. It is not true that all chemicals cause cancer even at maximum doses of administration.
- Carcinogenesis and mutagenesis are characterized by a self-replicating irreversible cellular change. The natural history of neoplasms, with few exceptions, is to grow irreversibly.
- All chemicals presently known to cause cancer in man (with the exception of arsenic) have been also shown to cause cancer in animals. Most of this evidence is derived from bioassays in rodents.
- Pathological development of chemically-induced tumors in experimental animals and in humans is very similar and most of the major types of cancer seen in human pathology can be reproduced in animals by chemical induction.
- The long latency period of cancer, its frequency in the population, and the difficulty in characterizing chemical exposures in populations and in identifying control groups which are not exposed to certain chemicals hinders epidemiological research. With chemicals to which exposure is nearly ubiquitous in the population, it is extremely difficult if not impossible to detect a specific carcinogenic effect in the population.

• The use of animal experiments to test chemicals for potential carcinogenic hazard to humans has been so far the only method accepted by the scientific community as reliable and adopted by public policy-making agencies in the United States. Short-term methods for the induction of neoplastic transformation of cells in culture presently show great promise as predictive screening tests but are not yet sufficently validated.

• Mice, rats, and hamsters are the experimental animal species of choice for carcinogenesis testing because their relatively short lifespan permits lifetime testing within a period of two to three years, and because tumor pathology in these species is well known.

• Chemical carcinogens do not appear to be specific in their effect only for one animal species. When extensively studied in different species of laboratory animals, chemicals which are carcinogenic in one species usually appear to be also active in others. The organs and tumor types involved in the carcinogenic response may not be the same under different test condition,s or in other strains, or in other species (including humans).

• The human population is genetically highly heterogeneous and therfore likely to have much more individual variability in susceptibility than laboratory animal populations, which are obtained from closed breeding colonies or even selectively inbred. It is the population subgroup more highly susceptible to carcinogens that requires the highest level of environmental protection.

• Current bioassay protocols for long-term carcinogenesis bioassays in animals are relatively insensitive, since they are usually designed to detect only levels of tumor induction higher than 5% or 10%. Negative results obtained in such tests are grossly inadequate to give assurance of safety for humans. Chemicals that are detected as positive in such tests are therefore, in this sense, "strong" carcinogens.

• No method is known for establishing a no-effect level of exposure to a carcinogen for humans.

• The implication of carcinogenicity should be drawn both from tests resulting in tumors diagnosed as benign and from those resulting in tumors which are more obviously malignant for the following reasons:

a. When adequately studied, virtually no chemicals are known to cause exclusively benign tumors and never to cause malignant tumors.

b. Many benign tumors may become malignant and there is evidence that in many cases the induction of histologically benign tumors is merely a stage in the induction of malignancy.

c. Benign tumors can pose serious health risks as such, even without becoming malignant.

d. If the exclusively benign nature of the tumor response were to be established, in most cases extensive microscopic analysis should be undertaken to rule out the presence of metastatic spread by multiple sections of all tissues which could be reached by tumor cells migrating from the primary tumor.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NO1-CM-67053

Title: *Development and production of parenteral (Task I) and oral (Task II) dose forms for clinical use*

Deadline: *Nov. 14*

The projects will entail preformulation, development, testing, packaging and labeling of investigational dosage forms for human trial. All products are to be prepared in accordance with good manufacturing practices. Proposal will be accepted for either the parenteral (task I) or oral (task II) projects.

Contract Specialist: Thomas Hardy
Cancer Treatment
301-427-7463

CONTRACT AWARDS

Title: Maintain an animal holding facility and provide research services

Contractor: Pharmacopathics Research Laboratories, Laurel, Md., $125,605.

SOLE SOURCE NEGOTIATIONS

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

Title: Management of conference on the genetics of human cancer

Contractor: Courtesy Associates.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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