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CLEARINGHOUSE EXEC. SECTY. SAYS IT HAS FAILED IN ITS OBJECTIVES, RECOMMENDS IT BE DROPPED

James Sontag, who as executive secretary of the Clearinghouse on Environmental Carcinogens is the NCI staff member most closely associated with it, has concluded that the Clearinghouse has not achieved its objectives and should be allowed to expire when its charter is up May 5.

"I believe the objectives for which it was created could be more effectively achieved through alternative mechanisms. I therefore suggest that consideration be given to the dissolution of the Clearinghouse," Sontag wrote in a memo to acting Div. of Cancer Cause & Prevention Director Gregory O'Conor.

Sontag analyzed in the 11-page memo the Clearinghouse' perform-

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In Brief

DCCP DIRECTORSHIP DRAWS 100 NAMES; UPTON AGREES CENTERS PROGRAM NEEDS MORE STAFF

WORLDWIDE INTEREST has been stimulated in the position of director of NCI's Div. of Cancer Cause & Prevention. The search committee headed by Div. of Cancer Treatment Director Vincent DeVita expects to receive more than 100 names, including some non-U.S. scientists. NCI has been advised that U.S. citizenship need not be a requirement for the job. . . . **CENTERS PROGRAM** director is another job NCI is trying to fill. It's been vacant since Simeon Cantril left more than 18 months ago. NCI Director Arthur Upton told *The Cancer Letter* he felt "it is important to stabilize the Centers Program, and leadership is the key." He said he agreed that the program should have more staff support. Some NCI executives have urged that the program be taken out of the Div. of Cancer Research Resources & Centers and be made responsible directly to Upton. The NCI director said that suggestion and others recommending it be moved to other NCI divisions are still under review. Also still under consideration is whether to upgrade the program director to a GS-16 level. DCRRC deputy director William Walter has been acting Centers Program chief since Cantril left. . . . **ROBERT HUEBNER**, chief of NCI's Laboratory of RNA Tumor Viruses since 1968, has retired but will continue his work there as an expert consultant. Stuart Aaronson, head of the lab's Molecular Biology Section, moves up as lab chief. . . . **FIRST CANCER** treatment unit designed specifically for the hospitalized teenage patient was opened last week at Roswell Park. Developed with the aid of a $337,000 grant from NCI's Div. of Cancer Control & Rehabilitation, the 10-bed unit includes facilities for recreation, dining, studies and patient and family counseling. Patients will be encouraged to entertain visitors in their own age groups and to utilize a study center containing books, periodicals and other educational aids.

O'CONOR, BROWN AGREE CLEARINGHOUSE SHOULD BE CONTINUED, FOR THE PRESENT

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ance in relation to six objectives. It was a critical review, not entirely negative.

"I thought it was a good memo, thoughtful, provocative, with merit in many of the things he said," O'Conor told ***The Cancer Letter.*** But NCI will not take any immediate action on the recommendations, O'Conor said. Appointment of a new DCCP director, decisions on directions in which the division will go, and the future of the Carcinogenesis Testing Program are all matters which probably will have to be settled before the fate of the Clearinghouse is determined.

"I recognize that the Clearinghouse is not perfect, but it serves a useful purpose," O'Conor said.

Primary function of the Clearinghouse is to advise the NCI director on recommendations he should make, to the public and to the regulatory agencies, as the result of information generated by the Carcinogenesis Testing Program. To do that, the Clearinghouse has considered the selection of chemicals to be tested, the design of the tests, evaluation of data produced by the tests and an assessment of risk to humans.

Among the questions to be answered, O'Conor said, is whether there is a need to put more than 70-80 new chemicals a year into the NCI bioassay program. If so, should NCI have the major responsibility or should other federal agencies assume the routine testing of chemicals and let NCI concentrate on research?

O'Conor said the Clearinghouse definitely would be continued beyond the May expiration date, perhaps with some revision in its membership, its objectives and organization of its subgroups.

Arnold Brown, chairman of the Dept. of Pathology & Anatomy at the Mayo Clinic who serves as chairman of the Clearinghouse, also believes it serves a useful purpose and should be continued.

"Jim raised some interesting points, and his position was carefully thought out," Brown said. "My view is that as long as there is a Carcinogenesis Testing Program at NCI, considering its economic and societal implications, broad public representation on the group that reviews those tests is appropriate.

"If carcinogenesis testing is moved elsewhere, then whatever remains—carcinogenesis testing research—would not require Clearinghouse activity but more of a scientific, technical review," Brown continued.

Here's how Sontag assessed the Clearinghouse performance on each objective (edited somewhat to conserve space):

Objective 1—Public concern about environmental carcinogens.

"It was hoped that through open discussion of the relevant issues and associated problems the public would gain a better understanding of the utility of animal models to detect potential human carcinogens.

"The Clearinghouse has touched upon most of the major issues. Generally, however, the discussions have tended to obfuscate issues rather than clarify them. An exception was a presentation by Dr. Robert Squire on the biological nature and significance of the mouse liver lesion.

"A major concern regards the most effective means of conveying an understanding of carcinogen bioassay to the general public. Since the general public cannot attend Clearinghouse meetings (*Ed. note:* they are all open and anyone may attend—Sontag was referring to the physical limitations), it must rely upon the news media. Representatives from the trade and lay press are among the more than 150 entries on the Clearinghouse mailing list. Despite this fact, neither the mouse liver lesion issue nor any other has sparked the interest of the press. It would not appear that the general public has become more cognizant of the issues as a result of Clearinghouse discussions. In fact, the public seems to be more perplexed than ever, although this cannot be attributed to the Clearinghouse.

"The major beneficiaries of news from the Clearinghouse would appear to be the very industries concerned with the chemicals under consideration. Representatives of the trade press, who regularly cover Clearinghouse meetings, usually report chemicals recommended for test and conclusions reached on individual bioassay reports. Other matters reported are often misinterpretations of the tone and tenor of discussions. By and large, factual information divulged at Clearinghouse meetings would be available upon demand to the public and private sections directly from the Program."

Sontag concluded that "as a means of providing the general public a better understanding of the issues involved in carcinogen bioassay, the Clearinghouse has not been successful."

Objective 2—Greater program openness.

"In concert with the prevailing trend (in government), it seemed that the creation of the Clearinghouse could contribute to greater Program openness," Sontag said.

"Clearly, the advent of the Clearinghouse has resulted in greater public scrutiny of the Program. The Clearinghouse ha s not always presented the Program in the most favorable posture. A major concern must be that the Program is not unfairly criticized to the point that its image becomes distorted in the public's view. Integrity and credibility is as important to the Program as it is to a bioassay study.

"Among the Clearinghouse subgroups, the most vocal criticism has come from the Data Evaluation/-Risk Assessment Subgroup. The validity of the criticism is often dependent upon one's knowledge, understanding and perspective of the Program. Although there have been instances of blatantly un-

justified criticism, it is reflective of individual members and not the Clearinghouse per se.

"The NCI carcinogen bioassay program represents the nation's major effort to identify and evaluate environmental carcinogens. Its public prominence, however, is due less to its size than to its sensitive nature. Thus, openness in the Program's operation and conduct is not only necessary for public accountability but also to assuage the public's concern that identification of environmental carcinogens is not being ignored."

Conclusion: The quantity of critical comments "leave little doubt that the Clearinghouse has resulted in greater Program openness."

Objective 3—Community participation.

"The bioassay effort impacts on a number of definable societal communities. Although each community avows its commitment to public health, approaches and perspectives to the problem differ. Thus it was thought that the Clearinghouse would provide a formal means for the relevant communities to have a direct input into the Program on issues that confront each individually but impact upon them all."

The Clearinghouse is made up of representatives from academia, organized labor, industry, public interest groups, state health departments and other public health related organizations. Each has had the opportunity to present its perspective on the major issues, Sontag noted. "Although it is questionable whether the Program or the communities have profited as a result of the direct input, the creation of the Clearinghouse has undeniably presented opportunities for collaboration."

Sontag concluded that the value of the participation would vary from one community to another, and that the value to the program "must be assessed directly by the staff."

Objective 4—Scientific and experience base.

"It was hoped that the Clearinghouse would afford the Program the opportunity to draw upon the practical experience of its members. At the same time it was hoped that a membership would be established whose technical expertise could bolster the Program's own scientific base."

At the time the Clearinghouse was established, the Program faced a critical shortage of professional staff, Sontag said. "Since then a large number of new positions have been allocated to environmental carcinogenesis. Thus, the need to bolster the scientific base of the Program in terms of manpower should no longer be a critical factor.

"A remaining issue concerns the scientific and technical contribution of Clearinghouse members beyond that already made by the Program staff. An estimation of that contribution could be guaged based on a comparison of the amount of advice given by the Clearinghouse to that accepted by the Program. Although I am not in a position to assess the latter, in my view only a modicum of substantive advice, over and above the confirmation of Program initiatives, has been rendered by the Clearinghouse."

Sontag concluded that the overall contribution to the scientific and experience base of the Program "is of questionable significance, particularly when compared with the expenditure of effort."

Objective 5—Advisory committee role.

The Program had no formal advisory committee when the Clearinghouse was established. It was intended that it would serve in that capacity, advising on both technical matters and on ones of more general Program concern.

"The two most active subgroups, Chemical Selection and Data Evaluation/Risk Assessment, have developed their own agenda items on which they consider advice should be rendered. These have not always coincided with those considered to be the most important by the Program. Despite differences, the bottom line must be measured in terms of the amount of constructive advice provided to the Program. Although what constitutes constructive advice is like beauty, for practical purposes the final judgment must be with the Program.

"A major impetus for the Clearinghouse concerned the backlog. Dr. Rauscher said it would play a major role in expediting the completion (of the analysis of tests and writing of the reports) of 210 chemicals constituting the backlog. That was based on the experience of the Program in preparing its first technical report on trichloroethylene. It was the opinion at that time of Program staff that technical reports should be subjected to the same peer review as were scientific articles in the open literature. the TCE report was sent to 15 experts around the country for ad hoc review. Each reviewer evaluated the report in the context of his own expertise without the benefit of joint consultation or discussion, without being able to question Program staff, and with different levels of understanding of Program objectives and operations. The staff had to meld the 15 individual reviews.

"It was apparent that this peer review procedure would be totally unworkable for the more than 200 reports that had to be prepared. Thus, one of the advisory functions of the Clearinghouse was to serve as a standing peer review group for the evaluation of bioassay reports. The Clearinghouse has filled this role, although one may question the quality of the review.

"If Program policy remains unchanged in regard to peer review of bioassay reports, the most efficient and effective means of conducting such reviews is through a standing review group. It may be that the policy is no longer necessary because of the current mechanism for preparing reports and/or their straightforwardness. In any case, peer review of bioassay reports is a factor that deserves attention in considering the fate of the Clearinghouse.

"It was hoped that the Clearinghouse would play a major role in nominating chemicals for test. To date, however, only a single nomination has come forth. The Clearinghouse has been particularly insistent in its intent to develop approaches for systematically examining the chemical universe and for rank ordering selections, though acceptable schemes have yet to be realized. Although these intentions are admirable, they are not entirely compatible with the role of an advisory group and are contrary to suggestions of the inhouse Chemical Selection Working Group. The latter has taken the tack that the Clearinghouse should advise on schemes under development by the CSWG rather than attempting to devise ones independently. The value of the Clearinghouse in the chemical selection process is reserved for the Program staff to judge. However, the need to have the Clearinghouse or any other nongovernmental group involved in the chemical selection process is a matter that requires reassessment.

"In the area of experimental design, the Clearinghouse has made few, if any, concrete suggestions as to improvements in methodology. It has conformed that the present procedure for the conduct of the prechronic toxicology, an area of some controversy, is reasonable given the current objectives of the Program. A topic that has stirred considerable discussion and involves experimental design concerns the issue of human risk assessment. Some members have adamantly insisted that the Program should design studies that would yield more data on which risk assessments could be based. However, it is necessary for the Program first to define its goals in the area before the associated experimental design problems can be addressed. Despite the human risk issue, the Clearinghouse is content with the presently used methodology, given the current Program objectives.

"The originally envisaged objective of having the Clearinghouse advise on the human risk of chemicals found to be animal carcinogens, in retrospect, was an overly ambitious one. Without a mass of complementary information, it is clear that the bioassay data alone are inadequate for any statement beyond one which notes that a chemical may pose a carcinogenic risk to humans. It would surpass presently available resources to collate and evaluate the needed complementary information necessary for a better defined risk assessment. Thus, the need for the Clearinghouse is greatly diminished with respect to its role in making risk assessments.

"At a recent meeting, the Clearinghouse was charged (by Director Arthur Upton) with the responsibility of advising on the Program's scope and direction, as well as other areas. Although there are many eminently qualified members capable of providing the advice requested, there is a question as to whether the structure of the Clearinghouse lends itself to the undertaking. Small working groups would need to be constituted to address areas to be reviewed. Reports of the working groups would be presented to the entire Clearinghouse for discussion and acceptance. Although unanimity may not be a reasonable expectation from any committee, the chances of getting any substantive reports accepted by even a simple majority may be questionable given the number and nature of the members."

Sontag said the Clearinghouse has cost NCI so far about $90,000, mostly members' travel costs and perdiem expenses. This excludes NCI staff support, which he estimated would add another $60,000 if salaries were to be charged to the Clearinghouse operation.

Sontag concluded that the Clearinghouse "generally has not been effective as an advisory committee. An exception may be in its function as a peer review group of bioassay reports."

Objective 6—Dialogue mechanism.

"It was considered appropriate for NCI to serve as a setting where representatives of adversary communities could meet and discuss issues relating to environmental carcinogenesis. It has been successful in bringing together those communities; it is doubtful that a true dialogue has developed between them. The issues of most importance are those on which there are few hard data to support a claim one way or another. As a result, each community considers its viewpoints as the correct ones."

Sontag concluded with these recommendations:

- "Given the performance of the Clearinghouse, it would not appear to be effectively achieving the objectives for which it was created. I would visualize no useful purpose of extending the charter beyond its present expiration date. If a decision is made to extend the charter, consideration must now be given to the selection of new members, since the terms of the original appointees expire in June."
- "An advisory committee to the Carcinogenesis Testing Program is both desirable and prudent. It thus would be expedient to establish a new Program advisory committee should the Clearinghouse be dissolved."
- The need to provide the public a better understanding of the issues involved in carcinogen bioassay is among the most important objectives of the Clearinghouse. This objective might still be met through a series of small workshops on specific issues. The end product of each would be a document that could be summarized for the public's use. The document also could be used in planning future Program direction."

Some Clearinghouse members feel that they contributed significantly in at least one way: Clearing up the infamous backlog did not get off the ground until the Clearinghouse applied the pressure.

"Some Program staff were recalcitrant and even obstructive," one Clearinghouse member said. "It took the prospect of embarrassing questions we might ask at open meetings to get them moving."

TEN MORE CHEMICALS SELECTED FOR TEST; SUBGROUP SAYS INDUSTRY SHOULD PAY

The Clearinghouse Chemical Selection Subgroup has recommended 10 more chemicals for the Carcinogenesis Testing Program, including two from the epoxide class to which large numbers of industrial workers are exposed.

The subgroup also approved a policy resolution calling on FDA to make every effort to require manufacturers to pay for tests. The resolution said:

"In those instances where a drug or other regulated chemical is recommended for carcinogenicity testing under the bioassay program, FDA should first pursue all legal procedures to place the burden of that testing on the manufacturer or manufacturers."

The NCI Chemical Selection Working Group already had recommended four epoxides for bioassay, largely because of their wide use, exposure in the workplace and among the general population, and because of the feeling of some group members that government regulation could take place based on inadequate information.

The chemicals recommended for testing are:

1,2 epoxybutane, 1,2 epoxyhexadecane, glycidol, methapyrilene, tetracycline hydrochloride, d-limonene, n-nitrosodiethanolamine, methyl carbamate, isophorone, and hexachlorocyclopentadiene.

Verne Ray, Pfizer Medical Research Laboratory and a member of the subgroup, noted that epoxides are mutagenic when tested in vitro. Subgroup Chairman David Clayson, Eppley Institute, said the class is important because of the environmental impact and because of the apparent catalytic ability of epoxides to activate vinyl chloride.

Ray said that glycidol is used as an intermediate in the manufacture of glycerin, as a germicide in pharmaceuticals and cosmetics, and as a sterilant in foods. NIOSH reported that 105,000 workers are exposed.

Methapyrilene is a non-prescription drug used as an antihistamine and in remedies for poison ivy and oak. Clayson said he was especially sensitive to the possible carcinogenicity because of its direct and purposeful human exposure. He recommended testing with a high priority using Henry Pitot's system of testing after exposure to a known hepatocarcinogen on a two-state model as a liver promoting agent.

Subgroup member William Lijinsky, Frederick Cancer Research Center, recommended it be tested by itself in the standard bioassay and with nitrite. He strongly supported dual testing because he felt some scientists might not accept data produced without the animal bioassay.

William D'Aguanno, FDA, said his agency had asked NCI to examine the drug in short term tests, which were negative. A later but questionable 18 month rat study was negative. Because of the questions, FDA feels another study is needed.

John Davitt, FDA, reported that tetracycline hydrochloride is the most widely used tetracycline compound. In one test, a newer tetracycline, minocycline, showed an increased incidence of thyroid tumor in rats. The drug class has hepatoxic potential and has a definite effect on the thyroid.

Clayson estimated the per capita use at a gram per year. Prescreening and carcinogenicity data are lacking and previous tests of compounds in the class class are inadequate and inconclusive, Clayson said. He concluded it should be tested with a relatively high priority.

Subgroup member Paul Ts'o, Johns Hopkins Univ., said it should be tested because of widespread use, direct human contact and previous inadequate animal tests.

J.F. Douglas, NCI, reported that Chemical Selection Working Group agreed that d-limonene should be tested because of its public exposure, inadequate previous testing, and its chemical structure.

R. Scheublein, NCI, reported that FDA is concerned about n-nitrosodiethanolamine because it is a nitrosamine, a reported hepatic carcinogen, and comes into contact sometimes in a prolonged manner with 200 million Americans. Because it is a cosmetic product, the law places the burden of proving it is a hazard on FDA. Previous tests will not stand up in court, Scheublein said, preventing FDA from taking regulatory action.

Lijinsky said that it has low toxicity and is extremely difficult to purify. Subgroup member Norton Nelson, New York Univ., said evidence of its carcinogenicity was well established but recognized the need for testing because of the legal problems. Clayson said he felt the compound might be overtested. Peter Magee, Temple Univ. and a member of the Clearinghouse Experimental Design Subgroup, commented that epidemiological studies are in progress and expressed concern that it is not known that the compound causes cancer in animals. He supported testing to have animal data to compare with the epidemiological data.

Elizabeth Weisburger, NCI, reported that interest in methyl carbamate emanated from an IARC monograph which cited several carbamates as requiring more testing; this one was considered representative. She cited its large production and use in making permanent press resins and reported there is only fragmented animal data.

Clayson said it is closely related structurally to a known potent animal carcinogen, urethane. He was not enthusiastic about testing. Subgroup member Kenneth Wilcox, Michigan Health Dept., wanted to ascertain whether people are exposed by wearing treated clothes. The subgroup approved it for test but with a low priority.

Weisburger reported production of over 100,000 pounds per year of isophorone, with primary use in

resins and lacquers and an exposure of over one million industrially. There is little epidemiological, animal or metabolic information, she said.

Norbert Page, NIOSH, said that primary use of hexachlorocyclopentadiene are as intermediates in the production of flame retardants, pesticides and dyes. He said it is accumulating in the environment and does bioaccumulate in the food chain. It is a potent irritant and there has been no adequate carcinogenicity test. But Ts'o and Ray pointed out that its use is rapidly declining and testing may not be necessary. It was approved for test with a medium priority.

The Clearinghouse Experimental Design Subgroup addressed the issue of designing tests more suitable for use in determining human risk assessment.

Cipriano Cueto, NCI, pointed out two facets of the problem—projection from one species to another, and extrapolation from high dose to low. He expressed concern that risk assessment is being conducted with data which was not developed for that purpose. He called for development of useful dose-response curves.

Clayson said that many scientists feel three doses might produce a meaningful dose-response curve. Magee commented that overall dose might be more meaningful than a dose-response curve. The question arose as to how the regulators could use this information, particularly in view of the diversity of their opinions regarding the number of doses.

Richard Griesemer, director of the Carcinogenesis Testing Program, pointed out that another question is the route of exposure as it relates to extrapolation from animals to man. Clayson said a weakness in extrapolation is one of monovariable exposure of animals compared with multivariable human exposure.

The subgroup unanimously approved a proposal by subgroup member Paul Nettesheim, NIEHS, that short term tests for genotoxicity and transformation should be routinely performed on all substances as a part of bioassay.

The full Clearinghouse, at its meeting last November, passed a resolution calling for use of short term tests in selection of chemicals to be tested, design of tests and evaluation of results.

Subgroup Chairman Marvin Kuschner, SUNY (Stonybrook), suggested that future advances in the ability to use information yielded by short term tests may make their present use even more valuable.

Ray said that short term tests could be especially useful in providing genotoxicity and malignant transformation information for interpretation of equivocal bioassay results.

The subgroup considered adding metabolic studies to the program, but Griesemer said this would considerably increase the costs. Subgroup members expressed a lack of confidence in the utility of such tests and agreed to defer any action on the issue.

The subgroup discussed effects of cyrstalluria but agreed not to request that tests for it be made part of the routine bioassay.

Ray proposed further statistical study of the range of normalcy and tests of significance as to the degree of response necessary to declare something significant, but the subgroup displayed little interest in that area.

GROUP CHAIRMEN UNHAPPY OVER H & N CONTRACTS, NCI PROTOCOL REVIEWERS

Cooperative Group chairmen reacted sharply and somewhat bitterly to recent NCI actions which affected some of them at their semiannual meeting last month. They also displayed increasing apprehension over the mammoth review of clinical research the Div. of Cancer Treatment is planning for its Board of Scientific Counselors in the spring of 1979.

The displeasure arose from two contract programs which were offered to the groups—the Div. of Cancer Control & Rehabilitation's $3 million effort to involve more community physicians in cooperative group activities, and DCT's head and neck cancer RFP. The chairmen wer also unhappy over NCI's use of "disease coordinators" to review their protocols and a delay in approving at least one.

DCCR awarded contracts to six cooperative groups, averaging $500,000 each, to recruit community physicians into their membership. "The intent was to bring community physicians up to date with the latest technology in phase II trials," DCCR Director Diane Fink told the chairmen.

Paul Carbone, chairman of the Eastern Cooperative Oncology Group, said there is a feeling among many community physicians that patients do not want to participate in clinical trials. "My feeling is that good clinical research is the best medicine. . . . We need to get it across to the physician that to ask a patient into a clinical trial is not an admission he doesn't know what is going on."

James Holland, chairman of Cancer and Acute Leukemia Group B, said his members were confused by the Cancer Control Program. "They felt you would be receptive to the transmission of proven protocols to community practice. Then you said no. Do you want protocols that have been proven in the groups, or do you want ones carved out for DCCR?"

"Group protocols per se were not our main interest," Fink answered. "That is, to draw more physicians into clinical trials."

"That policy was given to us as the reason for rejection (of CALGB's contract proposal). The group protocol was said to be not feasible for practice."

Fink said that was a decision of the technical review committee which reviewed the proposal and was not a policy of DCCR. "I don't think we will

get hung up on protocols. I see this as a happy marriage of the cooperative groups and cancer control, of a demonstration program and a classic clinical research program."

Holland also was unhappy because his group was not successful in competing for one of the head and neck cancer clinical trials contracts.

Last year when DCT Director Vincent DeVita asked his Board of Scientific Counelors for approval of his plan to award as much as $1 million in head and neck cancer contracts, Holland (a member of the board) argued vociferously in favor of channeling at least half that to the groups. DeVita agreed to let the groups have a shot at it, but resisted earmarking any specific amount for them. Instead, he said they could compete with all others on an equal basis.

Six groups responded to the RFP and submitted proposals, but only two were deemed "technically acceptable." Holland admitted that his group was told its proposal was not technically acceptable.

Franco Muggia, director of DCT's Cancer Therapy Evaluation Program, said 23 proposals had been received, nine were found technically acceptable and two of those were from the groups. "We're negotiating now to determine if we can fund all nine," Muggia said.

"What does technically acceptable mean?" Holland asked.

"Apparently, all four national multidisciplinary cooperative groups are not technically acceptable," commented Barth Hoogstraten, chairman of the Southwest Oncology Group and chairman of the chairmen's committee.

"Isn't there anything to be gained by the collective intellect, the variety of input and concepts the groups can offer?" Holland asked. "I sure would like to hear the ground rules for what is technically acceptable."

"We have 5% of our membership as members in the surgical society, yet were not technically acceptable," said John Durant, chairman of the Southeastern Cancer Study Group.

DeVita explained that "technically acceptable" was a term used in the contract review process to describe proposals that were considered for funding. Sometimes the term used to describe rejected proposals is that they are "not competitive." Proposals are ranked by priority, and those below a certain line are called "technically unacceptable" or "not competitive."

"That doesn't mean a surgeon is technically unacceptable," DeVita said.

Muggia said the reviewers decided one protocol could not be funded because it involved inoperable patients.

Holland argued that there are no biostatisticians on the review committees. "Without that, the advantage of multi-institutions is balanced out."

"If you feel there was unfairness in the review, we will re-examine it," DeVita said.

"Four major groups did not make it," Hoogstraten said. "I will challenge that. Yes, they were not reviewed adequately. We've been told it would not be considered further."

"There is an appeals process," Holland said. "I feel the groups can make a greater contribution than any single institution."

"I disagree," DeVita said. "The groups have a dismal record in head and neck cancer."

"There is no single good place in the country in head and neck cancer," Hoogstraten said. "We did what the RFP asked. We got radiotherapists, chemotherapists, surgeons, only to hear that we were not technically good enough."

"That was just a relative term," Muggia insisted.

"It is not correct that the groups have not done anything in head and neck," said Simon Kramer, chairman of the Radiation Therapy Oncology Group. "RTOG has done some major work, with 1,400 to 1,500 potentially curable patients."

"Simon has not received a letter, so you can assume he is technically acceptable," DeVita said.

"I haven't been home in a few days and don't know what's in the mail," Kramer said. "RTOG has shown that small dose preoperative chemotherapy remarkably reduces distant metastasis. Individual institutions have shown that preoperative radiotherapy is better than none, not the groups. You're not right in saying individual institutions have not made a contribution."

"I didn't say that," Holland said. "I believe there is enough collective intellect and skills in a group. You get a better picture, you get a half dozen people on a protocol, you get better information, better results than one man or one institution. A machine might be 5% off. That balances out with a group."

"You're being heard," DeVita said. "We'll take a look at it. I hope this doesn't mean that if we do this again and the cooperative groups fare poorly, it will always be because the review process is no good."

"I don't like this talk 'next time,' " Holland said. "The next time, we ought first to see if the groups can do it."

"There won't be a next time," DeVita said. "Head and neck is different."

"There will be a next time," Hoogstraten said. "So far, we have learned zero, other than that I am technically incompetent."

The chairmen bristled when the discussion moved on to DCT's "disease coordinators."

"What can he tell us we don't already know?" Hoogstraten asked.

"If there are five protocols already. He won't be telling you what to do, but hopefully can help reduce duplication," DeVita said.

"I say bring the five protocols, not some junior man's concept of duplication," Holland said.

"Who decides if a protocol is acceptable?"

Holland asked.

"Dr. Jacobs," Muggia answered. Ted Jacobs, administrative officer in the Clinical Investigations Branch, is in charge of protocol review.

"A one man decision," Holland said. "We're not totally ignorant of what is going on in other institutions."

Jacobs responded that the process is still in the developmental stage.

"Perhaps it will go out of existence," Holland said.

"I guarantee you it won't," DeVita said. "This was one of the Potomac Conference recommendations. No one person, myself included, will decide on protocols. But we need this review."

Carbone said that protocol review, which had been considerably improved and speeded up at NCI over the last two years, is slowing up again. "We've had a protocol here two months, with no feed back. I don't care what kind of protocol it is, if you get enough people looking at it, it will be rejected. Give us some flexibility. Okay, if there is gross duplication, stop it. But we're the research arm of NCI. Let us have some flexibility."

Carbone said his protocol was not turned down on the basis of science but on the issue of whether 5-FU is the standard treatment for colon cancer. "Let the cooperative groups coordinate themselves. If you try to do it from here, you are trying to direct us too damn much."

DeVita agreed that the "best protocols come from the groups, not us. The fact is, the best input is from the groups, and always will. You're right. Coordination has a bad ring to it."

"If you can't decide on whether to approve a protocol in a certain length of time, let us go ahead." DeVita agreed.

"This is critical," Holland said. "No single man on your staff, with a few years experience, ought to be permitted to counteract collective hundreds of years of group experience."

"Get your facts straight," Hoogstraten said. "NCI has never approved or disapproved a protocol."

"I have a letter of disapproval," Holland insisted.

DeVita said that on that one, the disease coordinator did not make that decision alone, "I agreed with him. Also, you can't substitute 100 years of experience for 20 years of brains."

DeVita told the chairmen that the review of clinical research next year would include all NCI supported research that involves human subjects—the groups, DCT supported contracts, clinical research conducted by other NCI divisions and grant supported clinical research.

"We are at a historical turning point in therapeutic research," DeVita said. "We're struggling now to put it all together. We're faced with the problem that if we were to start a clinical trials program today, would we set it up as we did 20 years ago?

"I assure you, neither I nor the staff are doing this because we are unhappy with the cooperative groups," DeVita continued. "The cooperation of the cooperative groups since they were moved to DCT has been outstanding."

Holland said he had some reservations "about the jury"—the Board of Scientific Counselors. "There is a hostile attitude toward clinical research on the part of some distinguished people on the Board. Some feel it is grossly overfunded."

DeVita disagreed. "The board is eminently reasonable. You shouldn't be fearful of what will happen. It is the best body we have to look at clinical trials."

CONTRACT AWARDS

Title: Immunological and biochemical studies of mammalian viral oncology, continuation
Contractor: Meloy Laboratories, $529,624.

Title: Application of animal virus model systems to human neoplasia, continuation
Contractor: Litton Bionetics, $235,095.

Title: Metropolitan Atlanta SEER Program
Contractor: Emory Univ., $439,882.

SOLE SOURCE NEGOTIATIONS

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

Title: Support services for studies on the application of animal virus model system to human neoplasia
Contractor: Litton Bionetics.

Title: Repository for storage and distribution of reagents, sera, and tumor specimens
Contractor: Flow Laboratories Inc.

Title: Support for a Cancer Surveillance System
Contractor: Fred Hutchinson Cancer Research Center.

Title: Inter- and intraspecies identification of cancer cells in vitro
Contractor: Child Research Center of Michigan.

Title: Role of viruses in experimental oncogenesis and human cancer
Contractor: Hazleton Laboratories America.

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Upton Moves Most Grant Programs To Divisions

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The NCI reorganization was announced to the staff Tuesday afternoon, after this week's issue of *The Cancer Letter* had gone to press. This supplement was prepared to immediately alert readers to this important news development.

Centers Program May Be Moved; DCRRC Left With Administration

NCI Director Arthur Upton stunned his staff this this week with the announcement of perhaps the most significant and far-reaching reorganization in the institute's history—the transfer of most existing grants and grant awarding authority from the Div. of Cancer Research Resources & Centers to NCI's program divisions. The Cancer Centers Program may also be moved from DCRRC to Upton's office.

DCRRC thus will be left primarily with the administrative end of the management of extramural activities. The reorganization includes the shift of all peer review responsibility, including contracts, from the program divisions to DCRRC.

The Research Facilities (construction) Branch will remain with DCRRC, as will, for the present, the Organ Site Program.

The reorganization will give the Div. of Cancer Biology & Diagnosis, Div. of Cancer Cause & Prevention, Div. of Cancer Control & Rehabilitation, and Div. of Cancer Treatment authority over grants in their respective program areas. Until now, they have been able to support extramural research only through the contract mechanism and through Cancer Research Emphasis Grants, which are sort of a hybrid of grants and contracts.

The reorganization will be welcomed by the division directors and program directors. Others, chiefly the DCRRC staff members involved, are apprehensive, as will be many in the scientific community who fear that it will further impinge on investigator initiated research.

DCT Director Vincent DeVita told cooperative group chairmen recently that, if he had had access to the grant mechanism, he probably would not have awarded contracts for clinical trials.

However, Upton said in his announcement of the change that "as a rule, basic research will be supported either intramurally or through grants; other than basic research, either intramurally or through contracts."

Among advantages of the reorganization cited by Upton were that it would strengthen the program divisions and encourage reprogramming of contract research dollars to grants.

Upton's announcement follows:

To improve the scientific, management and training activities of the National Cancer Institute and to bring it into conformance with other institutes of NIH and in compliance with HEW review and evaluation policies, and to give grant applicants a better chance to compete, the following staff, funds, functions, grant portfolios and other resources will be transferred from DCRRC:

1. Biology Branch to Div. of Cancer Biology & Diagnosis.
2. Cause & Prevention Branch to Div. of Cancer Cause & Prevention.
3. Organ Site Program Branch to Div. of Cancer Treatment (*perhaps—see below*).
4. Clinical Manpower Branch partially to Div. of Cancer Control & Rehabilitation and partially to Div. of Cancer Treatment.
5. Research Manpower Branch as appropriate to DCT, DCBD, and DCCP.
6. Diagnosis & Treatment Branch to DCBD and DCT.
7. Cancer Centers Program to Office of Director.

(Upton still had not definitely made up his mind about moving the Centers Program but was expected to do so momentarily.)

Abolished as organization entities will be the Biological Research Program, Training & Education Program, and Centers & Treatment Program.

Retained in DCRRC will be the Review & Referral Branch, Research Analysis & Evaluation Branch, Grants Administration Branch, and Research Facilities Branch.

Transferred to DCRRC will be staff, funds, functions and other resources of:

1. Office of Committee & Review Activities from DCCR.
2. Collaborative Research Branch of the Viral Oncology Program in DCCP.
3. Office of Coordinator for Collaborative Research of the Carcinogenesis Research Program in DCCP.
4. All personnel, functions and resources of each division other than DCRRC with 75% or more of their duties and responsibilities directed toward peer review as executive secretaries of peer review groups.

5. Responsibility for creation, abolishment, selection of members, and management of all contract and grant peer review groups of NCI.

6. Certain staff (to be identified) of the Research Contracts Branch in the Office of Administrative Management whose responsibilities encompass development and issuance of policies relating to NCI contracts.

A Contracts & Grants Policy Branch will be established in DCRRC, charged with responsibility for establishing and overseeing institute policies governing use of all grants and contracts.

The Organ Site Program Branch, its programs, staff and responsibilities will be retained in DCRRC pending further consideration of long term management needs of this program and its most appropriate locus.

Advantages the reorganization will bring, as claimed by Upton:

"Establishes clearer focus and closer alignment with related science management programs.

"Facilitates program management and fiscal planning by focusing management attention on program rather than mechanism; strengthens program divisions by providing greater access to grants and training mechanisms.

"Encourages reprogramming of contract research dollars to use for grants by consolidating authority for budgeting of related programs under division directors with the full range of mechanism options.

"Facilitates recruitment by allowing prospective science managers to focus on program rather than mechanisms.

"Conforms to HEW policies which require separation of review and grant management activities from program management activities.

"Relieves program managers of time demands as peer review executive secretaries.

"Provides increased attention to and direction of the Centers Program by the institute director."

Another advantage listed (and which failed to impress some staff members) was that the reorganization "conforms closely with the organization which has proved successful" at other NIH institutes.

NCI division directors and their program managers have long felt that it did not make sense to deny them use of grants as a funding mechanism. Former Director Frank Rauscher agreed, feeling that if investigator initiated grants could be gathered under a program's wing, the program director could fill in any gaps either with contracts or CREGs and could eliminate undesirable duplication. But Rauscher never attempted to implement that feeling, deferring to those who felt it would lead to too much "directed" research.

King, although anything but pleased by the reorganization, said he would do his best to make the transition as smooth as possible, in transferring the science programs to the other divisions.

One of the concerns of grantees and their allies is that the divisions adopt uniform policies in reviewing applications and awarding and administering grants. They fear that one division might fund its grants to a low priority score while another might have a cutoff at a much higher one. That and other inconsistencies could frustrate and discourage scientists to the point where they would drop out of cancer research, some feel.

On the other hand, if large sums of money now going into contracts actually are diverted to traditional grants, it would go a long way toward overcoming those fears. "Provided it is handled in a fair and even manner," one scientist said. "Otherwise it could be a disaster."

Commercial firms—life science industry, as they refer to themselves—might also be wondering where they will come out in this. Some of them are engaged in basic research under NCI contracts. But HEW regulations forbid awarding of grants to commercial organizations. They can be expected to renew their efforts to get that regulation changed if it appears most research contracts will be phased out in favor of grants.

No time has been established for implementation, although NCI staff members feel it will move ahead rapidly now that the basic decision has been made.

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Is an insert to?
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