THE CANCER NEWSLETTER

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SHORTAGE OF PATIENTS IN RIGHT PLACE, TIME DEVELOPS AS MAJOR PROBLEM FOR INVESTIGATORS

There are an estimated 500,000 new cancer patients each year, but clinical investigators are experiencing serious problems in lining up sufficient numbers of them in the proper categories, in the right places and at the right time.

A shortage of patients was not one of the problems anticipated by NCI but it ranks with the always-present problem of limited funds among difficulties facing investigators, members of the Cancer Treatment Advisory Committee were told this week. The committee held a two-day meeting at NIH.

Tests for new drugs and new drug combinations, combined modalities, new radiation sources, and immunotherapy have increased dramatically as the impact of the massive increases in the cancer program has made itself felt. Each of these have made increasing demands on patient resources.

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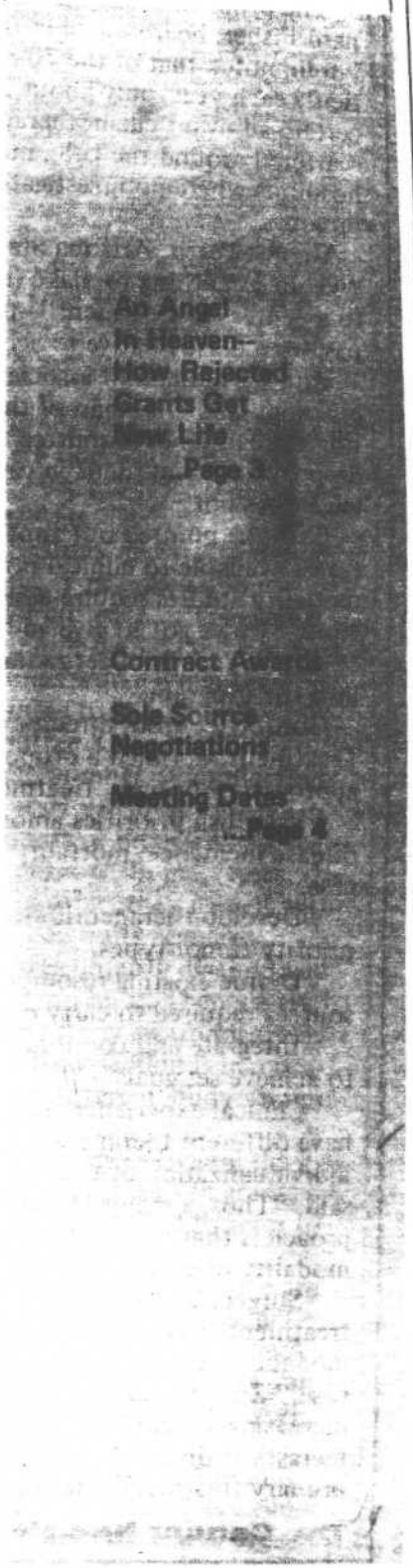
IN BRIEF

HEW CLAMPS DOWN ON FORMER EMPLOYEES HIRED TO GO AFTER JOBS THEY HAD HELPED DEVELOP

NEW REGULATIONS proposed by HEW deals with the hiring of former HEW employees and putting them to work trying to land HEW contracts or grants. The proposed rules, published in the May 1 *Federal Register* would: bar noncompetitive grants or contracts to an organization which employs or is negotiating with former HEW employees "in circumstances which constitute a real or apparent conflict of interest;" require organizations seeking competitive grants or contracts to notify the department whether it employs or is negotiating with a former HEW employee; ban noncompetitive awards to organizations with former HEW employees on their payrolls who are involved in developing applications or proposals concerning subjects in which they participated personally and substantially as an agency employee, or who are involved in managing any contract or grant in their former subject area as a government employee. Even if the employee is not involved in securing or managing the contract or grant, the organization will not be eligible if his job at HEW involved for the year before he left the same subject matter. Secretary Weinberger said the requirement that applications for contracts and grants must report any previous HEW employment "for the first time would allow us to determine whether any possible favoritism exists before the fact—a point vitally important to the integrity of the system". . . .**UNIV. OF MARYLAND** hospital will get NCI's clinical research facility being moved out of the Baltimore PHS hospital. The new arrangement offers "an enormous opportunity to get into combined modality therapy for solid tumors," said Gordon Zubrod, director of NCI's Div. of Cancer Treatment. . . .



COMBINED MODALITY THERAPY PROMISING, BUT UPS DEMAND FOR MONEY, PATIENTS

(Continued from page 1)

Immunotherapy protocols especially have sharply increased the need for more patients in clinical investigations. "The immunologists are waiting at the hospital doors, grabbing the patients as they come in," one committee member said.

The problem is basically a geographical one. Bernard Fisher, board member from the Univ. of Pittsburgh, noted that of the 70-80,000 breast cancer patients each year, only about 20,000 are suitable for certain adjuvant chemotherapy protocols. They are scattered around the U.S., most of them in smaller hospitals where no investigations of that type are in progress.

George Pettit, Arizona State Univ., suggested that "we do something to make it more attractive to come to a center for treatment"—travel expenses, per diem pay for a close relative to accompany the patient.

Paul Carbone, NCI associate director for medical oncology and chairman of the Breast Cancer Task Force treatment committee, said that some contracts do provide travel funds in cases where patient insurance does not.

Carbone pointed out another growing drain on funds available to clinical investigators: combined modality studies require additional professional services. "We've got to give additional funds to the cooperative groups to get radiotherapists and surgeons into the program."

Gordon Zubrod, director of the Div. of Cancer Treatment, outlined a proposed combined modality approach to primary treatment:

—Establish priorities among tumors on the basis of disease incidence, mortality and probability of success.

—Develop therapeutic strategies for the highest priority tumor types.

—Define existing resources and develop new resources required to carry out the program.

—Integrate and coordinate all treatment resources to achieve set goals.

"Clinical experience suggests that different diseases have different therapeutic requirements necessitating individualization of treatment strategies," Zubrod said. "Thus, a major feature of the proposed approach is that it must be disease-oriented rather than modality oriented.

"Surgery and radiotherapy applied as primary treatments have the highest curative potential of all modalities in solid tumors without disseminated disease," Zubrod continued. "However, it is becoming increasingly clear that undiagnosable microscopic metastatic disease foci already exist at the time of primary treatment. This imposes an upper limit to the curative potential of surgery and radiotherapy since these modalities cannot affect tumor cells in distant sites.

"Eradication of the last neoplastic cell requires systemic treatment. Chemotherapy and possibly immunotherapy can kill neoplastic cells anywhere in the body and, hence, have the potential for destroying all metastatic foci of early disease. It is observed that chemotherapy and/or immunotherapy are maximally effective at the time when the tumor cell population is small (early in the disease or after surgical removal of the primary tumor mass). Localized and systemic modalities are, therefore, therapeutically complimentary.

"Accordingly, the proposed approach provides for integration of local and systemic therapy modalities into appropriate strategies for primary treatment of specific diseases," Zubrod emphasized.

The proposed approach for increasing cure rates in solid tumors involves the following sequential strategy:

—Test independently new surgical, radiotherapeutic, chemotherapeutic and possibly immunotherapeutic procedures in cancer patients as early as is ethically permissible.

—Integrate optimal single modality regimens for primary treatment of disseminated disease.

—Integrate optimal single modality regimens into a combined modality approach for primary treatment of local and regional disease.

Zubrod was critical of "the plurality of intramural and extramural approaches presently underway for identical diseases and the lack of coordination among these various thrusts. This overlap is not only costly, but it is often counter productive," he said.

An example he noted was in breast cancer therapy. Intramural contract programs are underway in Zubrod's division; six cooperative groups supported by the Div. of Research Resources & Centers have similar studies ongoing; and the Div. of Cancer Biology & Diagnosis is supporting an extensive therapy program through the Breast Cancer Task Force.

"A plurality of efforts is not necessarily wrong, since no single group has a monopoly on good ideas regarding therapy," Zubrod said. "What is unfortunate is the existence of overlaps, the absence of standard protocols for identical disease situations, the dispersion of already limited clinical resources, the lack of uniform definitions and data reporting techniques, poor coordination and inadequate exchange of information, all leading to excessive exposure of patients to investigative therapy as well as to decreased operational efficiency.

"Many attempts have been made in the past to develop coordinated approaches among the various intramural and extramural groups involved in cancer

treatment," Zubrod charged. "With rare exceptions, they all have failed. Each group continues to pursue its own goals. Even in breast cancer where best positive evidence for coordination exists problems still abound despite continuous intensive efforts."

Zubrod asked the committee for its suggestions on how to attack the problem.

"I have great confidence in the scientific elements and approaches outlined," said Clifton Mountain, board member from M.D. Anderson. "The administrative structure is the crucial problem. Is that our job (to resolve)?"

"It is fair game for the committee to take up anything it pleases," Zubrod answered.

AN ANGEL IN HEAVEN—OR HOW REJECTED GRANTS DO AND DON'T GET RE-REVIEWED

(At the March meeting of the National Cancer Advisory Board, some members expressed concern about consideration that may or may not be given to grant applications that had been either disapproved by *study sections, assigned such low priority that they had no chance for funding, or funded inadequately. The following discussion (edited here to remove irrelevant material) was taken from a tape recording of the meeting. Participating in the discussion were NCI Director Frank Rauscher, Board Chairman Jonathan Rhoades, Univ. of Pennsylvania; Harold Amos, board member from Harvard; Benno Schmidt, chairman of the President's Cancer Panel; Palmer Saunders, NCI director of the Div. of Research Resources & Centers; Sol Spiegelman, board member from Columbia; and Arnold Brown, board member from Mayo Clinic)*

RAUSCHER: What mechanism does NCI have to take a relook at grantees who have been turned down or approved without adequate funding? You've all had letters circulated to you (from unhappy applicants). We need to assure Congress of the objectivity of peer review and that the system is working and working well.

RHOADS: (Recounted history of dual review at NIH, in which advisory councils frequently overturned decisions of study sections). There was too much reversing of primary reviewing body decisions. Finally the councils were told that they could reject an application that had been approved for funding (by the study sections) but could not fund any rejected by the primary reviewing body.

An investigator could question now whether most reviews are single, or do we really exercise dual review.

(Rhoads suggested that NCI staff could refer cases where there is some indication of unfairness or mistaken rejection to an NCAB subcommittee. The subcommittee would review the application and then bring it to the board for an up or down recommendation)

If that is a suitable procedure, would someone make a motion that we adopt that as board policy?

AMOS: That is not a suitable solution. We have dealt with a number of applications which we were not prepared to deal with. (Amos described some weaknesses of the study section system, and referred to examples of unfairness or inadequate review). Not everyone who complains is a sorehead. Some applications ought to go back for regularly constituted, multidisciplinary review.

RHOADS: Bring the questionable ones to the subcommittees, which would make the recommendation to re-review or not.

SCHMIDT: How do you determine which ones are questionable? Do we do it on the basis of whether or not the guy writes me, as some do, or writes (Congressman) Paul Rogers? If so, you probably would be re-reviewing some of the worst. If it's on the basis of who makes the most noise, then you would have to re-review every reject. Just how would you decide which turndowns are deserving of this extra review?

AMOS: Make some rules. Maybe a single turndown would not be sufficient.

SAUNDERS: We've been doing exactly what you suggested. Program directors are responsible for reviewing all grant applications we recieve from study sections, including the disapprovals. They go over each summary statement very carefully and try to detect any evidence of those things you talked about—where a man has been either cut back or assigned a low priority because they didn't understand his work or were not sympathetic to his work. When they identify these, they bring these to the attention of the (appropriate) subcommittee. Over the last two years we've gone over a large number of applications of these sort, in which the staff has pointed out discrepancies, unfairness, amounts of money awarded too low to accomplish the purpose. In may cases, the subcommittees concurred; in some, they agreed with the study sections. This goes on quite regularly.

If we feel an application was unfairly disapproved, we ask the board to defer action on it. Then we try to get it re-reviewed by the same study section if there is new information, or if that study section is inappropriate, we ask for review by a different study section or by several study sections.

AMOS: But there are several instances (where the system described by Saunders did not result in grants to deserving investigators, and Amos started to refer to an individual)

RHOADS: Let's not discuss individuals here. We are all aware of the example you cited. While it is inefficient to have a policy greasing the squeaky wheel, sometimes it is necessary. These kinds of things don't happen frequently, but when they do happen, you have to pay attention to them.

SCHMIDT: There's a question of whether the subcommittees are constituted properly to sit as a super

study section. Or whether subcommittees constituted outside the board may be better qualified for re-review.

RHOADS: Most can give a competent over-all review, objectively.

SAUNDERS: There is another mechanism that's not been used since the inception of the National Cancer Advisory Board. Summary segments are forwarded to board members prior to meetings so they can detect what they suspect to be miscarriages of justice in evaluation and call it to our attention. The last two or three meetings there has not been a single contact from a board member concerning these summary segments.

AMOS: We're not competent to make a judgement from a summary sheet.

SCHMIDT: If you saw a rejection of a man you knew was absolutely A plus and was not likey to be making a grant application without knowing what he was doing, that in itself would be suspect.

SPIEGELMAN: I've known a case where a very bad decision was made involving a very bright and engaging man, but I sort of hesitated at the principle of having an angel in heaven in your court.

BROWN: Did you read the grant application?

SPIEGELMAN: I sure did.

BROWN: Was it that good?

SPIEGELMAN: Yes. It damn well was good. An injustice was done.

BROWN: There was no excuse for you to be silent under those conditions.

SPIEGELMAN: I was not silent as an individual. I did speak out. I was silent as a board member. I thought that I should not exercise that kind of clout.

RHOADES: What kind of clout do you think a board member has? (Laughter)

SPIEGELMAN: I hesitated to test it.

RAUSCHER: Sol, in your judgment on that particular application, if it had been funded, would the National Cancer Program been that much better?

SPIEGELMAN: Of course.

RAUSCHER: Then you have to bring it up, and having an angel in heaven has nothing to do with it.

SOLE SOURCE

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

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

Title: Maintenance of rodent production centers
Contractors: Harland Industries, Indianapolis; ARS/Sprague-Dawley, Madison, Wisc.; Charles River Breeding Laboratories, Wilmington, Mass.

CONTRACT AWARDS

Title: Training programs for maxillofacial prosthedontists and maxillofacial dental technicians
Contractor: New York Dept. of Health and Health Research, Inc., Roswell Park Memorial Institute, $273,907

Title: Synthesis of unique compounds for cancer chemotherapy studies
Contractor: Midwest Research Institute, Kansas City, Mo., $1,469,854 (continuation)

MEETINGS

NCI advisory group meetings frequently are closed, usually for review of contract and grant applications. Times scheduled as open will be shown with each listing, but these sometimes are changed.

Cancer Special Programs Advisory Committee, NIH Bldg 31, conference room 8, May 9-10, open May 9, 9-10 a.m.

Spontaneous regression symposium, Baltimore, May 9-10.

American Federation of Clinical Oncologic Societies, New York City, May 13.

American Cancer Society Conference on Childhood Cancer, Dallas, May 16-18.

Cancer Centers Review Committee, NIH Bldg 31, conference room 6, May 17-18, open May 17, 9-10 a.m.

President's Cancer Panel, NIH Bldg 31, conference room 5, May 20, 9:30 a.m.-12, all open.

Virus Cancer Program Scientific Review Committee, Landow Bldg, conference room C418, May 29, open 9-10 a.m.

Cancer Control Education Review Committee, NIH Bldg 31 conference room 3, May 31, open 8:30-9:30 a.m.

The Cancer Newsletter—*Editor* JERRY D. BOYD

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