THE CANCER LETTER

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CLINICAL EDUCATION GRANTS HELD TO 170 PAYLINE, NO NEW AWARDS; ORGAN SITE RENEWALS LIMITED TO 180

The impact of budget restrictions along with the determination of NCI Director Vincent DeVita to reduce or phase out programs which he feels have accomplished their purposes was reflected in decisions by the institute's Executive Committee last week on funding the Clinical Cancer Education and Organ Site Programs in the current fiscal year. The committee, which includes the NCI director, deputy director, associate directors and division directors, agreed to:

–Establish the payline for competing renewals in the Clinical Cancer Education Program at a priority score of 170 and not fund any new grants.

–Fund competing renewals in the Organ Site Program to a 180 pri-

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In Brief

BURKITT, EPSTEIN WILL DIVIDE BRISTOL-MYERS AWARD; "ITALIAN NOBEL" WON BY COLUMBIA'S SOL SPIEGELMAN

BRISTOL-MYERS Award for Distinguished Achievement in Cancer Research this year was won by Denis Burkitt and Michael Epstein for their discoveries which led to the identification of the first virus regularly linked to human cancer. Burkitt identified the tumor known as Burkitt's lymphoma, the most common childhood cancer in much of Africa. Working with Burkitt's lymphoma cells, Epstein isolated the Epstein-Barr virus. The two will share the $50,000 prize. . . . **SOL SPIEGELMAN**, director of the Institute for Cancer Research at Columbia Univ., has received the 1981 Antonio Feltrinelli International Prize in Biological Sciences. Sometimes known as the "Italian Nobel," the prize is worth 100 million lire (about $83,000). The award citation credits Spiegelman with studying "almost all functional aspects of DNA and RNA and of discovering phenomena of central importance in molecular biology". . . . **FDA CAN FURTHER** improve its adverse drug reaction reporting system, the General Accounting Office has reported following a review of that system. "Many adverse reaction reports do not get to the division maintaining the system and many others require a long time to get into the system," GAO said. "Some of the missing or late reports involved serious reactions which were not discussed in the drug labeling. Reporting by nonmanufacturer sources, such as hospitals or physicians, could also be increased." GAO recommended that FDA require medical officers to attend seminars and workshops on the adverse drug reaction system, solicit ideas on how the system could be improved, consider dropping from the system reporting of known, nonserious reactions, and explore using a toll free or collect call service to encourage reports from nonmanufacturer sources.

FOUR COMPETING CLINICAL EDUCATION RENEWALS OF 31 APPROVED TO BE PAID

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ority score, and not fund any new ones at this time. In the past, NCI did not hold this program to a payline but permitted funding to the extent of the budget.

The current payline for traditional (R01) grants is 180. Holding the clinical education renewals to 170 and not funding new ones will free up more than $1 million.

The Clinical Cancer Education Program has been considered by NCI executives and reviewers to be an excellent one, funding about 80 institutions a year to support development of coordinated approaches to teaching cancer treatment techniques to medical students.

The program's budget for 1982 originally was $5.8 million. Of that, $4.6 million is required to fund 66 noncompeting (type 5, continuing) renewals. If the remaining $1.2 million were left in the program, it would fund competing grants up to priority scores of 201-202.

As it is, with the 170 cutoff, only four competing renewals will be paid, those with scores of 141, 149, 155, and 170. One new application scored 156 but will not be funded because of the policy against new starts in the program. Thirty-one competing grants were approved by the Clinical Cancer Education Review Committee, 28 with scores better than 250. Three scored between 170 and 180.

The decision to fund at the 170 payline may not be final. Since only three more grants would be funded if the payline were to be moved back to 180, the budget impact would be minimal and NCI would be acting in a more even handed manner. About $1 million would still be available for reprogramming. Some new organ site grants might be funded if more money becomes available.

The education program was cut back two years ago when support for graduate training was dropped. One of the program's major successes was encouraging the training of medical oncologists; so successful, some feel, that there now are or soon will be too many practitioners of that specialty.

DeVita also has argued that the program has successfully demonstrated the value of coordinated cancer treatment teaching and that medical schools should carry on those efforts without NCI support.

The National Cancer Advisory Board Subcommittee on Organ Site Programs will meet next week to consider what steps to take following the review of the projects and recommendations of the ad hoc review committee (***The Cancer Letter,*** Feb. 5 and 12).

DeVita has submitted his recommendation to NCAB Chairman Henry Pitot, and there will be others which the subcommittee will consider. At the NCAB's meeting in February, an effort to in effect dissolve the program was rejected but probably will come up again.

That effort, led by NCAB member Janet Rowley, would have returned review of Organ Site Program grants to the NIH Div. of Research Grants. Those grants now are reviewed by the working cadre of the four projects, and the review group suggested that since many of the working cadre members are grantees themselves in the program, the potential exists for conflicts of interest.

Some Organ Site Program participants agree that the program should be separated from review, as were most other programs when former NCI Director Arthur Upton reorganized the institute four years ago. However, they are holding out for review by NCI study sections in the Div. of Extramural Activities, as are the cancer center, cooperative group, cancer control, program project, and education grants. They argue that this would help preserve the coordination and communication elements of the program.

The ad hoc committee report said members reaffirmed the value of conducting research targeted to specific organ sites, and recommended that the program be continued with cost reductions by combining services including review and discontinuing large scale clinical trials.

The committee made no choice in changing the review system between NCI-DEA and NIH-DRG, recommending only that the process "be streamlined" with either one review committee for all four, or one each for bladder-prostate and for bowel-pancreas, or use of NIH study sections.

The committee did recommend that management should continue to be decentralized with headquarter institutions outside of NCI and "attempts should be made to restore the diminishing autonomy of the projects."

ACS ENCOURAGING RESEARCH PROPOSALS ON PSYCHOSOCIAL ASPECTS OF CANCER

The American Cancer Society is encouraging research proposals on the psychosocial aspects of cancer because "today's challenge requires expansion of programs to improve the quality of life for patient and family," President Robert Hutter and Board Chairman Allan Jonas said in a joint statement in the society's annual report this week.

The growing number of patients who are recovering from cancer is bringing about subtle but important changes in the overall approach to the cancer problem, ACS leaders indicated in the report.

Arthur Holleb, ACS' chief medical officer, stressed the need for better psychological backup of cancer patients and their families. "Coping is the most important because we are curing more patients than ever before, and when cure is not possible, produc-

tive life is being extended," Holleb said.

Hutter and Jonas also revealed that the society is committed to a stronger activist role. "Finding the causes and cures for cancer are medical and scientific problems," they said, but "eliminating the causes—prevention—may well be personal, social and political problems. If you have any doubt about this, just think about cigarette smoking and cancer. The society's new role in public issues and cancer must be one of an aggressive advocate of prevention."

ACS already has 2,300,000 volunteers in 3,128 community units, but plans to increase the number of units in 1982. It will place renewed emphasis on door to door programs of fund raising and education, and its successful outreach to black Americans will now be followed by similar outreach programs for hispanics and native Americans.

Reviewing scientific progress of the past decade, Frank Rauscher, the society's senior vice president for research, described the nation's expanded attack on cancer as "the most important, intensive research program in the biomedical history of any nation . . . and also one of the most successful."

According to the report, fiscal 1981 was a record year for the society. Total income reached $200 million for the first time. Of this amount, $170,408,203 came from campaign contributions, special events, memorial gifts and legacies. Most of the remainder came from interest on funds designated for program use.

TASK FORCE FINDS DRUG DEVELOPMENT EFFECTIVE, OFFERS RECOMMENDATIONS

The HHS Task Force charged with investigating and reporting on NCI's development of anticancer drugs and the Food & Drug Administration's regulation of them concluded that "recent NCI and FDA changes are positive and reflect efforts to improve management of the anticancer drug development program. The implementation of these changes and the recommendations of the Task Force will help to correct existing problems as the agencies continue to carry out effectively their respective roles. The Task Force believes that cancer patients have been aided and will in the future benefit from the anticancer drug development program."

The Task Force report is in two volumes, the first intended as a summary and the second in greater detail. The report cites no major deficiencies on the part of either NCI or FDA but does note some "weaknesses" and suggests some remedies.

NCI is preparing a formal response. Vincent DeVita, who was intimately involved with the various controversies surrounding the Drug Development Program, before and after he became director of the institute, wrote an informal 32 page response. He dished up some criticism of his own:

"In general, the summary of the conclusions of the Task Force are reasonable and identical in both volumes," DeVita wrote. "One might say that they do not quite match statements made in the text. The main criticism, in my view, is that the report represents the entire process as a 'frozen image' at one point in time, rather than a dynamic, evolving, experimental drug development program that often is faced with a pleasant paradox—each success creates a new set of problems. The price of avoiding problems is therefore too high. The success in solving these has been considerable, but one does not get this impression from the report.

"There are no recommendations which NCI has not already implemented or is unwilling to implement, although in some cases we would argue that they represent redundancies built into the system to assure that any future Task Force would find its job a little easier."

The Task Force summarized its findings:

"NCI's anticancer drug development program is a complex, unique scientific and therapeutic endeavor focused on one facet of cancer research and treatment, while FDA's Bureau of Drugs has the role of regulating NCI's new drug development to ensure that unacceptably dangerous drugs are are not used in the treatment of cancer in humans. These two agencies operate on the frontier of science and medicine to develop chemotherapy for more than 100 forms of cancer.

"The Task Force assumed its charge with recognition of the pressure on NCI to succeed in the development of new drugs and the necessity that FDA ensure the timely approval of safe and effective new drugs. Against this background, and its deliberations, the Task Force concluded that:

"1. The new toxicology protocol has been judged to be sound by a satisfactory process, but continuing review is needed.

"2. A nationwide clinical testing program sponsored and supported by NCI has led to many chemotherapeutic agents now widely used in cancer. Approximately 40,000 patients annually survive because of these drugs. Some phases of the clinical trials need closer central management.

"3. Recently augmented controls on the distribution of anticancer drugs by NCI to its investigators are sound and should minimize or eliminate the problem of drug leakage.

"4. Within the limitations of the state of the art, NCI and FDA procedures for addressing adverse drug reactions are acceptable for protecting the cancer patient from unnecessary risks.

"5. Therapeutic intent exists in phase 1 clinical trials involving new anticancer drugs.

"6. Protection of the cancer patient through proper informed consent procedures can be improved by adherence to existing HHS and FDA regulations; the institution review board and the physician share

a major responsibility for the adequacy of the consent process, and, in that role, may be helped by educational material provided to them by the sponsor (NCI), the NIH Office of Protection from Research Risks, and FDA.

"7. The proper use of sanctions by both FDA and NIH is appropriate and needed against wrongdoing investigators and institutions.

"8. The memorandum of understanding is a useful document in which FDA and NCI incorporate further managerial and operational understandings that may facilitate the activities in the development and regulation of anticancer drugs."

DeVita was especially critical of the first volume of the report.

"It is strange to see this report divided into volumes I and II," DeVita wrote. "Purportedly, volume I is a summary document, volume II is not substantially larger but is a more complete and accurate account of the subject. Volume I, in general, emphasizes the negative aspects through implied assumptions, without any positive comments. Volume II gives a much more balanced view of the differences of opinion with backup information. In my view, a person trying to understand this entire process would have a difficult time getting a balanced view from volume I.

"The report fails to indicate whether opinions voiced are majority or minority. For example, comments such as 'lack of quality protocols from the NCI,' 'serious concern over chemistry of anticancer drugs' all represent minority opinion of FDA staff as judged from the instances given to NCI; yet they are given the full weight of an FDA opinion. This, of course, has been the problem with NCI-FDA interactions all along but it is difficult to perceive this from the report. One has only to look at the comments in reference to reasons for elevating the sign-off authority to the associate director in the Bureau of Drugs. In volume I this is handled in a very cursory fashion. From volume II it is quite clear that this was done because a few FDA division personnel were not performing adequately. The philosophical question which should be addressed is whether two or three staff members in either of the two organizations can obstruct a process developed by the majority of the staff and the communities they serve. This issue does not emerge in either document."

Recommendations and DeVita's responses follow:

Toxicology Protocol

Task Force—The value of the dog and mouse as predictors of qualitative toxicity, the value of dose escalations in dog in predicting cumulative toxicity, and the effectiveness of the proposed scheme for selecting a safe and efficient starting dose for humans should be reconsidered repeatedly in light of accumulating experience under the new toxicology protocol. A schedule for such reconsiderations should be drafted by NCI, as it would improve the chances that appropriate changes in the protocol will be made promptly, and would enhance the credibility of this important scientific and medical document. The updated new toxicology protocol—including contingencies for nonroutine testing (such as testing for possible cumulative toxicity and performance of animal histopathology prior to human testing), a description of how the results will be used to calculate the initial dose for humans, and the planned schedule for analysis of accumulating results—should be assembled and presented to the appropriate FDA and NCI advisory committees for approval.

DeVita—NCI is reconsidering all phases of the new toxicology protocol at frequent intervals. The first drugs developed under this protocol are just going into clinical trials. A schedule for reconsideration seems like window dressing since it is impossible to predict appropriate intervals with any degree of accuracy. NCI intends to monitor this protocol continuously in view of its importance to worldwide toxicology for anticancer drugs. NCI has presented an updated toxicology protocol. As revisions have been suggested, we have responded to these suggestions. It is not possible to present a final protocol until all the issues are settled. Some issues have been reviewed repeatedly by FDA staff by appeal. It should be pointed out that the issue of cumulative toxicity has been raised by NCI. The old protocol was inadequate to predict cumulative toxicity. The new protocol is not intended to predict cumulative toxicity. A completely separate protocol will be required for prediction of cumulative toxicity.

Clinical Trials

Task Force—NCI should develop and maintain a single, comprehensive, and updated description of its drug testing organization, its procedural requirements, and the responsibilities of investigators. Copies of this document should be made available to all investigators, centers, cooperative groups, and so on, and utilized in an expanded educational effort.

DeVita—The master file is the best document available for a single comprehensive and up to date description of NCI's drug testing organization, procedures, and requirements. An abbreviated version of this can be developed but, quite frankly, it is likely to be of less value because of its abbreviation. Individuals interested in the details of cancer drug development must be familiar with the voluminous material in the master file. A briefer description would be useful for any future task forces.

Task Force—NCI should require that every protocol include a clear statement of the number of patients to be studied as a condition for approval and that a proposal to amend the number be approved by the appropriate IRB(s) and NCI committee(s).

DeVita—This recommendation is unrealistic. The number of patients who enter phase 1 trials depends upon whether a single or multiple dose is tested, by different routes of administration, and different schedules. The number can vary from 30 to several hundred and will be changed as toxicity dictates a change in the dose and/or schedule. An estimate of the number of patients required, depending on the number of doses and schedule to be tested is a reasonable requirement, but is rarely accurate. To make rigid requirements for procedures to change the numbers would slow our efforts considerably.

Task Force—Each protocol should also show how patient accrual will be monitored as execution of the study begins and how accrual will be stopped when the approved sample size has been achieved.

DeVita—This is already done and was described in greater detail in volume II of the report. For phase 2 testing the number of patients adequate for clinical trials has also been misunderstood. All patients with a givien type of cancer present with multiple and different sites of involvement. Each site may respond differently to therapy. Given the fact that multiple schedules, doses and routes of administration are

tested in patients who present with multiple site, and with previous therapy further confounding the interpretation of results, it is unrealistic to require that a rigid number of patients be prescribed in a phase 2 study. In addition, one or two responses in a phase 2 study alter the number of patients required over the already unpredictable number.

Task Force–The quantity of drug that will be required to complete the approved protocol should be estimated at the outset, and the cumulative amount shipped under that protocol number should not be allowed to exceed the estimate without an explanation and a check of total patient accrual.

DeVita–NCI already estimates the quantity of drug required for each protocol. We do not usually send the full amount because this contributes to "leakage," since some patients do not live through a full phase 2 study. Surplus drugs are not always returned.

Task Force–NCI should conduct analyses of treatment results at appropriate intervals to define the degree to which the effectiveness of a drug in one tumor affects the probability of effectiveness in another tumor, and the results should be incorporated into the decision process that assigns priorities to phase 2 protocols.

DeVita–Clearcut evidence was presented to the Task Force that some drugs work in only a single tumor. As long as this finding is accepted, the fact that some do not respond to a series should not prohibit testing against a specific tumor for a specific reason.

Task Force–NCI's Investigational Drug Branch should take a position of clearly understood leadership in the execution of the requisite number of phase 2 drug tests on varying types of cancer, so that initial determination of the possible clinical efficacy of a drug will not be long delayed after the completion of phase 1. This recommendation includes the negotiation of additional clinical testing contracts, if necessary.

DeVita–NCI's IDB has already taken a clear position of leadership in all aspects of the execution of phase 2 testing. Investigators supported by the National Cancer Institute often regard this "leadership" as being too forceful and prefer greater leniency than is presently in the system.

Task Force–NCI should conduct a systematic analysis of the timeliness and appropriateness of the key decisions made by staff review groups such as the protocol review and decision network committees.

DeVita–We fail to understand the nature of this recommendation. It seems to derive from the fact that the Task Force did not understand the complicated system that NCI uses at various levels. In volume 2 all of the systems are described but there is confusion concerning the roles of the Cancer Panel and the National Cancer Advisory Board, the divisional boards of scientific counselors, and most importantly, between extramural peer review groups and intramural staff committees that make decisions about moving drugs along in the preclinical-clinical flow.

Task Force–IDB should develop procedures for prompt review of the clinical and administrative data problems, and findings of the Clinical Trials Monitoring Service, for implementing corrective action with investigators, institutions, or cancer cooperative groups, and for monitoring of the effects of such action upon the performance of the clinical trials.

DeVita–IDB already does this. The reason the Task Force was able to comment on problems in data collection is because the CTMS system has already identified such problems and NCI has responded to them.

Task Force–NCI should strengthen its clinical trials management activity promptly to add management oversight and enforcement capabilities to the current monitoring effort. This management group should be given responsibility for ensuring that researchers using investigational drugs under NCI sponsorship comply with approved study protocols, drug distribution policies, and ADR reporting procedures, as well as the requirements for annual reports, informed consent, and good laboratory practices. The activity can provide the information needed by NCI and its advisory committees to evaluate the success of the current research strategy and to compare it with modified or alternate approaches.

DeVita–The main reason for implementing the cooperative agreement mechanism in clinical trials by NCI was to specifically spell out the responsibility of NCI staff to investigators supported by grants. This is a very controversial area and this conversion has been done with due consideration to the sensitivity of the research community to retain as much flexibility as possible for innovation.

Task Force–NCI should examine the extent to which the clinical, laboratory, and pharmaceutical record systems can be linked and reconciled (through standardized records or even through computer coupling) with the drug distribution management system and the clinical trials information system. This would enhance NCI capability to facilitate the tabulation and analysis of data to support a later NDA; and to develop more systematic and efficient investigative and auditing practices, more effective management, and more complete and timely reporting.

DeVita–NCI has always worked in this direction.

Task Force–The Bureau of Drugs should include all of the NCI-sponsored drug investigators within their selection procedures of investigators and institutions for review on a routine basis. To the extent possible, FDA should utilize the results of NCI monitoring to minimize duplication and to utilize FDA inspectors in the regions to conduct the monitoring as is done for other drug monitoring.

DeVita–We do not disagree with this recommendation. It should be noted, however, the Task Force concluded that NCI is given no special treatment. The Bureau of Drugs has always monitored anticancer drugs to a lesser degree than other classes of drugs because of the unique circumstances involved. NCI is monitored as little as the industry.

Investigational New Drug Distribution and Investigators

Task Force–NCI should require: (1) that all investigators including those affiliated investigators practicing in satellites of cooperative group institutions and cancer centers be formally registered by a form FD 1573 either as individual investigators or listed as under the personal supervision of the principal investigator and a specific IND number. (This information should be made available to FDA to permit inclusion of all NCI investigators using NCI supplied chemotherapy in its strategy for selecting investigators for routine investigations); (2) that all drugs provided under a specified protocol for human use but not used in accordance with that protocol be returned to NCI for proper handling by the Pharmaceutical Resources Branch, DCT, NCI; (3) that communication links about eligibility to receive drugs and drug usage be developed among PRB and the appropriate other branches of DCT to control drug distribution and leakage effectively; and, (4) that under circumstances of noncompliance with NCI's requirements or FDA's regulatory requirements, no cytotoxic drug be shipped from NCI to the investigator.

DeVita–This recommendation is already followed by NCI. All drugs are required to be returned if unused as specified in Form 1573 (signed by the investigators). The problem of leakage is dealt with in the new system for monitoring drugs. However, it has always been clear that the investigator has a responsibility for returning unused drugs.

Task Force–NCI should develop a set of instructions or guidelines on drug handling responsibilities of investigators to be sent out once a year to every investigator who files an updated or new form FD 1573.

DeVita–NCI will be happy to do this. Nonetheless instruc-

tions and guidelines are already clearly spelled out in Form 1573 and in the guidelines sent to each physician with Group C drugs.

Task Force—High priority should be given to implementing the proposed NCI plans as soon as possible to remedy what is viewed as a serious defect in the current drug distribution system. Requiring such logs and reporting should both dissuade investigators from misuse of drugs and readily identify the practice of "secondary" distribution of investigational drugs, that is, the transfer of drugs to physicians outside the regulated environment and the use of investigational drugs for unapproved purposes.

DeVita—Plans have been implemented (January, 1982) for the logging in use of drugs distributed to investigators. The recommendation of the Task Force that a full supply of drugs be sent to investigators who have approved phase 2 protocols could actually increase leakage. It should also be pointed out that while leakage is not desirable, there is no evidence that drug leakage itself has caused serious problems.

Task Force—The Group C drug classification should be retained.

DeVita—We agree that the Group C classification has been useful and should be retained. It does cost the NCI considerable time, energy and resources and has saved the FDA a considerable amount of staff work.

Protection of Human Subjects

Task Force—NCI and FDA reviewers of informed consent forms should become more familiar with the required elements of the FDA and HHS regulations and use a reference review guide that lists the required elements of the regulations to ensure that the consent forms are thorough and specific and are evaluated against the requirements.

DeVita—NCI believes that its staff ought to be and are familiar with the elements of informed consent and DHHS regulations.

Task Force—Feedback from NCI and FDA review of informed consent forms should be made to IRBs and to investigators; FDA bioresearch monitoring inspections should categorize deficiencies in informed consent forms from site visits so that summary data can be compiled for educational activities and to provide needed feedback.

DeVita—This type of feedback does take place.

Task Force—IRBs should encourage lay members to review consent forms to determine that language is understandable and not unnecessarily technical, and encourage all members to use a review guide for review of informed consent forms.

DeVita—This is a good suggestion and is a positive step toward improving the informed consent forms. It should be noted that all IRBs have lay members who review informed consent forms.

Task Force—OPRR should develop an educational program for all participants in the consent process—sponsors, institution representatives, and investigators—to spell out their respective responsibilities, and methods to ensure maximum communications of the risks and benefits of participation in clinical trials.

DeVita—OPRR-NIH are sponsoring such educational programs.

Task Force—OPRR should: (a) proceed to select at random and review consent forms approved by IRBs; (b) expand the current review of grant summary statements for protection of human subjects to include NCI contracts; and (c) initiate reviews of investigators, IRBs and institutions to determine adherence to regulations.

DeVita—It is my understanding that OPRR is in the process of doing this.

Task Force—NCI should increase its operational ties with OPRR with regard to protection of rights of cancer patients.

DeVita—NCI's operation ties with OPRR are very close. The Task Force failed to point out that NCI is the only Institute on the NIH campus which not only approves informed consent forms of a study in advance, (after review and approval by IRB), but also has a CTMS contractor that checks to see that the informed consent form approved is the one actually used in the protocol.

Comparison of FDA-NCI Relationships with FDA-Industry Relationships

Task Force—BD should define the appropriate level of signoff responsibility for letters dealing with important regulatory matters and implement that decision consistently. The current inconsistency should be eliminated. Steps should be taken to ensure that division-level personnel perform effectively and with reasonableness and sensitivity to all sponsors in accordance with BD policy.

DeVita—We agree with this recommendation but believe that the difficulties with the performance of a minority of BD divisional staff was underemphasized in this volume.

Task Force—For purposes of resolving conflicting views within FDA and improving communication between NCI and FDA, a study should be performed regarding: (1) the characteristics of clinical protocols thought to be flawed by some FDA staff (which should result in methods to ensure higher quality of future protocols implemented by the NCI cytotoxic drug development program); (2) the characteristics of those chemical and purity reports on cytotoxic drugs thought inadequate by some FDA staff (which should result in agreement on the standards to be used in subsequent INDs); and (3) the allegations of some FDA staff of frequent and extensive absence of documents required for various parts of the investigational new drug program. The Task Force suggests that the responsibility for this effort be given to an organization other than NCI or BD.

DeVita—This recommendation is bothersome. There is an implied assumption that NCI protocols are flawed. This seems to be the view of a minority of FDA staff. "Flawed" refers to differences in the testing of cytotoxic drugs compared to other classes of drugs; this is better discussed in volume II. For example, phase 2 studies are never randomized controlled studies while there are often randomized controlled studies in non-cytoxic drug development. The issue of chemical purity is an important issue for only a minority of FDA staff who have been identified by FDA as overreaching their authority. In most cases the purity of compounds is not in question. This issue arose for a few specific drugs (laetrile was one) and was raised repeatedly by one chemist in particular. It seems to result in unnecessary work.

Communications Problems

Task Force—NCI meetings should be structured for free exchange of ideas on the science and medicine of cytotoxic drugs while insulating those discussions from FDA regulatory functions of attending FDA staff. Relevant information from such meetings should be submitted formally from NCI to specific FDA IND files. Regulatory issues should be addressed formally in writing and responded to in writing. The FDA and NCI communication channels should be used fully.

DeVita—NCI's meetings are currently structured to encourage free exchange of ideas on science and medicine. FDA staff have **never** been asked to perform regulatory functions while attending these meetings. Some FDA staff unilaterally decided not to attend these meetings, in spite of the fact that their attendance was an integral part of the MOU and the master file to monitor the process which NCI uses for drug development. The relevant information for these meetings is routinely submitted to appropriate FDA senior staff and should be submitted to the appropriate FDA files by the FDA staff. In volume II the minutes of these meetings are described as "superb" documents and should be more fully used by

FDA staff.

Task Force–BD should reexamine its surveillance pattern for field inspection efforts and consider placing cytotoxic INDs higher on the priority list.

DeVita–While we do not disagree with this recommendation, we think the policy in place in the FDA recognizes differences between cytotoxic and other kinds of drugs.

Task Force–In view of the allegations, the Office of the Assistant Secretary of Health's Office of Management should undertake a management study of the BD divisions and BD managers dealing with cytotoxic drugs to examine areas about which questions have been raised such as organization, personnel and staffing, budget, decision making procedures, internal communications, morale, workload, filing system, and paperflow.

DeVita–We do not disagree with this recommendation; however, the problems seem fairly clearcut and should not require a special task force.

Sanctions

Task Force–NCI should more actively impose sanctions against wrongdoers.

DeVita–NCI agrees that if wrongdoers are identified, sanctions should be imposed.

Task Force–NCI management officials should be reminded of their obligations to report violations of federal rules and regulations to appropriate law enforcement authorities, e.g., HHS Inspector General.

DeVita–We have been duly reminded.

Task Force–Sanctions should be considered against the institution as well as the individual wrongdoer when multiple violations occur at a single institution, when appropriate.

DeVita–Withdrawal of funds from an institution does represent such a sanction.

Task Force–45 CFR 74 should be amended to allow suspension or termination of a grant, not only for causes related to that grant, but for causes related to activities of the investigator in other context.

DeVita–This seems possible under current regulations but we do not disagree with this recommendation.

Task Force–The Director, NIH, should review the NCI procedures for denying investigators use of NCI sponsored drugs for clinical investigations to ensure that the procedures are fair and to provide for consistent treatment of investigators.

DeVita–The purpose of this recommendation is unclear.

Task Force–FDA and NIH should expedite development of plans and procedures for the sharing of information regarding ongoing and completed regulatory and monitoring investigations including the sharing of findings of wrongdoing with agencies and organizations (federal and nonfederal) outside HHS.

DeVita–This is a complex recommendation. Such information is shared, however, NCI, NIH and FDA have differing responsibilities.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR APRIL, MAY, FUTURE

Tumors Involving the Skin–April 1, Roswell Park continuing education in oncology.

National Cancer Advisory Board Subcommittee on Activities & Agenda–April 1, NIH Bldg 31 Rm 6, 1:30 p.m., open.

Oncology Update 1982–April 3, Biltmore Hotel, Los Angeles. Contact Sandra Rozzen, Northridge Hospital Medical Center, Education Dept., 18300 Roscoe Bldg., Northridge, Calif. 91328, phone 213-885-5311.

Possible Role of Nitrosamines in Human Cancer–April 4-7, Cold Spring Harbor, N.Y., contact Dr. Victor McElheny, 516-549-0507.

Genetic Mechanisms in Chemical Carcinogenesis–April 5-6, Univ. of North Carolina, Chapel Hill. Contact Mimi Minkoff, Cancer Research Center, Box 30, MacNider Bldg., Chapel Hill 27514, phone 919-966-3036.

Breast Cancer Task Force–April 5-6, NIH Bldg 31 Rm 6 on the first day, Rm 4 on the second, 8:30 a.m. both days.

The Eucaryotic Gene–April 5-7, Glasgow. Contact Dr. D.M.J. Lilley, Biochemistry Dept., Medical Sciences Institute, Univ. of Dundee, Dundee EE1 4HN, Scotland.

Special FEBS Meeting on Cell Function & Differentiation–April 10-14, Athens. Contact Dr. A.E. Evangelopoulos, National Hellenic Research Foundation, 48 Vassileos Constantinous Ave., Athens 501/1, Greece.

Symposium on Genetic Mechanisms of Carcinogenesis–April 11-15, Riverside Motor Lodge, Gatlinburg, Tenn. Contact Dr. W.K. Yang, Biology Div., Oak Ridge National Laboratory, PO Box 6, Oak Ridge, Tenn. 37830, phone 615-574-0700.

New Approaches in Colo-Rectal Cancer–April 14, Yale Univ., Mary S. Harkness Auditorium. For practicing physicians, nurses, health practitioners, and tumor registrars. Contact Office of Graduate & Continuing Education, Yale Univ. School of Medicine, PO Box 3333, New Haven, Conn. 06510, phone 203-432-4582.

Pediatric Hematology/Oncology for the 80s–April 15-17, Grady Memorial Hospital Auditorium, Atlanta. Contact LeRoy Pickles, Continuing Medical Education, Emory Univ., 319 WMCAB, Atlanta 30322, phone 404-329-5695.

Society of Surgical Oncology–April 18-23, Boston, 35th Cancer Symposium and Annual Meeting. Contact Dr. William Nelson, PO Box 1565, Manchester, Mass. 01944.

Rational Basis for Chemotherapy–April 18-23, Keystone, Colo. UCLA symposia on molecular & cellular biology. Contact Molecular Biology Institute, UCLA, Los Angeles 90024.

Congress of the European Society of Child Radiology–April 19-24, Prague. Contact Czechoslovak Medical Society, Vitezneho unora 31, 12026 Prague.

2nd European Conference on Reach to Recovery–April 22-24, Paris. Contact PMV Vivre comme avant, BP 246, 92205, Neuilly-s/Seine, France.

Oncology Nursing Society–April 23-25, Stouffer's Riverfront Hotel, St. Louis. Seventh Annual Congress. Contact ONS, 701 Washington Rd., Pittsburgh, Pa. 15228, phone 412-344-3899.

American Occupational Medical Assn. – April 25-30, Toronto. Contact Dr. David Muir, Scientific Program Chairman, Occupational Health Sciences Center, 3H50, McMaster Univ., 1200 Main St. W., Hamilton, Ontario L8N 3Z5, Canada.

American Society of Clinical Oncology–April 26-27, Stouffer's Riverfront Hotel, St. Louis. 18th annual meeting. Contact ASCO, 435 N. Michigan Ave., Suite 1717, Chicago 60611.

Computers in Radiation Oncology in Europe–April 26-28, Geneva. Contact R.J. Berry, Dept. of Oncology, Middlesex Hospital School, London W1P 7PN, UK.

American Assn. for Cancer Research–April 28-May 1, Stouffer's Riverfront Hotel, St. Louis. 73rd annual meeting. Contact Dr. Fred Philips, AACR, 1275 York Ave., New York 10021.

Lung Cancer Symposium–April 30, Cavalier on the Hill Hotel, Virginia Beach, Va. Sponsored by Chesapeake General Hospital, Western Tidewater Health Education Center, and Eastern Virginia Medical School. Contact Brunet Jean-Gilles, MD, Chesapeake General Hospital, PO Box 2028, Chesapeake, Va. 23320, phone 804-547-8121, Ext. 1119.

Society for Clinical Trials–May 2-5, Pittsburgh. Third annual meeting. Contact the society, 600 Wyndhurst Ave., Baltimore 21210, phone 301-435-4200.

Washington Imaging Conference–May 2-7, Washington D.C. Second annual meeting. Sponsored by Alexandria Hospital and American College of Radiology. Contact Susan Ferraro,

Dept. of Radiology, Alexandria Hospital, 4320 Seminary Rd., Alexandria, Va. 22304, phone 703-379-3102.

Course on Chemotherapy of Neoplastic Diseases–May 3-7, Stockholm. Contact Y. Gahrton, Karolinska Institutet, Huddinge Sjukhus, 141 86 Huddinge, Sweden.

Breast Cancer Update 1982–May 5, Overlook Hospital, Summit, N.J. Contact American Cancer Society, Union County Unit, 512 Westminster Ave., Elizabeth, N.J. 07208.

American Society for Head & Neck Surgery–May 5-6, Palm Beach, Fla. Annual meeting. Contact J.C. Goldstein, Div. of Otolaryngology, Albany Medical College, Albany, N.Y. 12208.

International Congress on Environment & Geocancerology–May 5-7, Brussels. 20th anniversary of the European Institute of Ecology & Cancer. Contact E.G. Peeters, rue des Fripiers 24 bis, 1000, Brussels, Belgium.

National Tumor Registrars Assn.–May 5-7, Orlando. Seventh annual meeting. Contact E. Shambaugh, Tumor Registry, State Dept. of Health, Richmond, Va. 23219.

NCI Div. of Resources, Centers & Community Activities Board of Scientific Counselors–May 6-7, NIH Bldg 1 Wilson Hall, 8:30 a.m. both days, open.

Controversies in the Management of Childhood & Adolescent Cancer–May 6, Roswell Park continuing education in oncology. Contact Gayle Bersani, Cancer Control Coordinator, RPMI, 666 Elm St., Buffalo 14263, phone 716-845-4406.

Assn. of Clinical Scientists–May 6-9, Santa Monica. 64th spring meeting. Contact Dr. F.W. Sunderman, Dept. of Laboratory Medicine, Univ. of Connecticut School of Medicine, 263 Farmington Ave., Farmington, Conn. 06032, phone 203-674-2328.

New Directions in Multimodal Treatment–May 7, Kaiser Center Auditorium, Oakland, Calif. Cancer of colon, rectum, and anus. Sponsored by Bay Area Tumor Institute. Contact Jeanne Hoek, 415-465-8570.

American Roentgen Ray Society–May 10-14, New Orleans. Annual meeting. Contact the society, Harper Grace Hospital, Dept. of Radiology, 3990 John R St., Detroit 49201.

In Vitro Mutagenesis–May 12-16, Cold Spring Harbor, N.Y. Contact Meetings Secretary, 516-549-0507.

Mechanisms of Resistance to Anticancer Drugs, 1: Antimetabolites–May 15, Univ. of California Medical School, San Francisco. Sponsored by the Northern California Cancer Program. Contact NCCP, PO Box 10144, Palo Alto 94303, or phone Martha Kaplan, 415-497-7431.

Fifth International Symposium on Prevention & Detection of Cancer–May 16-20, Sao Paulo. Contact the symposium, 05409 rua Oscar Freire, 239602 andar, Caixa Postal 11.490, Sao Paulo, Brazil.

National Cancer Advisory Board Subcommittee on Clinical Oncology & the Community–May 16, NIH Bldg 31 Rm 11A10, 7:30 p.m., open.

National Cancer Advisory Board–May 17-19, NIH Bldg 31 Rm 6, open May 17, 8:30 a.m.–3 p.m. and May 19, 8:30 a.m.–adjournment. Closed May 18.

Third World Conference on Lung Cancer–May 17-20, Tokyo. Contact Japan Organizing Committee for the Conference on Lung Cancer, National Cancer Center, Tsukiji, Tokyo 104, Japan.

NCAB Subcommittee on Review of the Office of Director Contracts & Budget–May 19, NIH Bldg 31 Rm 7, 12:30 p.m., open.

Alternatives to Mastectomy 1982: Conservative Surgery & Radiation as Primary Treatment for Early Breast Cancer–May 19-21, Cambridge, Mass. Contact Drs. Jay Harris, Samuel Hellman, or William Silen, Program Directors, Educational Resources Associates, Inc., PO Box 301, Newton, Mass. 02158, phone 617-738-8859.

International Symposium on Leukemia Cell Biology & Therapy–May 19-22, St. Jude Children's Research Hospital, Memphis. Sessions on etiology, hematopoietic cell differentiation, immunobiology, biochemical pharmacology, clinical trials and state of the art, new directions and future imperatives. Contact International Symposium, PO Box 318, Memphis 38101.

RNA Processing–May 19-23, Cold Spring Harbor. Contact Meetings Secretary, as above.

Div. of Cancer Biology & Diagnosis Board of Scientific Counselors–May 20, NIH Bldg 31 Rm 7, 9 a.m., open.

Div. of Cancer Cause & Prevention Board of Scientific Counselors–May 20-21, Bethesda Holiday Inn, Versaillles Room, 9 a.m. both days, open.

Radiation Carcinogenesis: Epidemiologic Approaches & Biological Significance–May 24-26, Bethesda, Md. Contact Dr. John Boice Jr., NCI, Environmental Epidemiology Branch, Landow Bldg. Rm 3C07, Bethesda, Md. 20205, phone 301-496-4153.

Flow Cytometry: Applications in Cell Biology–May 24-28, Rochester, N.Y. Fourth annual course. Contact Dr. Paul Horan, Course Director, Dept. of Pathology, Box 626, Univ. of Rochester Medical Center, Rochester N.Y. 14642, phone 716-275-5516.

FUTURE MEETINGS

Frontiers in Cancer Therapy–June 3-4, New England Deaconess Hospital, Boston. Sponsored by Harvard Medical School. Includes presentations on new directions in chemotherapy, ionizing and nonionizing radiation therapy, supporting therapy and surgical oncology. Contact Harvard Medical School, Dept. of Continuing Education, Boston 02115.

Radiation Therapy Oncology Group–July 19-21, Bellevue Stratford Hotel, Philadelphia. Contact Lawrence Davis, MD, Associate Chairman, RTOG Study Center, 925 Chestnut St., Philadelphia 19107, phone 215-574-3150.

Ninth UICC Training Course in Cancer Research–Oct. 10-21, Weizmann Institute of Science, Israel. Intended for postgraduate students in biochemistry, biology and medicine under age 35 who wish to specialize in cancer research. The course will be given in English. Contact before May 15 Prof. Gideon Berke, Dept. of Cell Biology, Weizmann Institute, Rehovot, Israel 76100.

Sixth Annual Scripps Cancer Symposium–Oct. 11-13, Vacation Village Hotel, San Diego. Sponsored by Scripps Memorial Hospital. Concurrent with Cancer Symposium for Nurses, Islandia Hyatt House, San Diego, also sponsored by Scripps. Contact Nomi Feldman, 3770 Tansy, San Diego 92121, phone 714-453-6222.

Nutrition and Cancer–Oct. 22-23, Univ. of North Carolina. Fifteenth Annual Malignant Disease Symposium, sponsored by the Clinical Cancer Education Program, Cancer Research Center, UNC, and the American Cancer Society North Carolina Div. Contact Dr. William Heizer, Cancer Research Center, Box 30, MacNider Bldg., Univ. of North Carolina, Chapel Hill 27514.

The Cancer Letter _Editor Jerry D. Boyd

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