THE CANCER LETTER

P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

Vol. 7 No. 48

Nov. 27, 1981

Subscription $125.00 per year

CHEMOPREVENTION CLINICAL TRIAL RFA BEING DEVELOPED FOR JANUARY CONCEPT REVIEW, ALONG WITH "BRIDGE" RFA

Investigators will be invited to submit grant applications for human chemoprevention trials if the Board of Scientific Counselors of NCI's Div. of Resources, Centers & Community Activities approves the concept of such studies when its meets Jan. 14-15.

The Board heard a report from its Chemoprevention Subcommittee at its meeting last month which recommended among other things that an RFA (request for applications) be developed for human trials. But DRCCA Director Peter Greenwald had been on the job for only a few weeks and there was no time to translate the committee's recommendations into an RFA.

Greenwald told *The Cancer Letter* this week that two RFAs will be presented to the Board for concept approval—one for human trials, the other for "bridge work" between laboratory and epidemiologic observations and their development into human studies, as suggested by Board member Harry Eagle.

Board Chairman Stephen Carter said the subcommittee had first felt that chemoprevention efforts should be done on the Biological Response Modifiers Program model, which is in the Div. of Cancer Treatment. "But we agreed it was not ready for that," Carter said.

(Continued to page 2)

In Brief

CT SCANNING REDUCES MORBIDITY, MORTALITY, HELPS DELIVER OPTIMAL TREATMENT, CONSENSUS PANEL SAYS

USE OF COMPUTER assisted tomography has resulted in detection of smaller lesions and more accurate localization of primary brain tumors, an NIH consensus conference panel concluded this month after three days of scientific assessment of CT brain scanning. Lower surgical morbidity and mortality and decreased length of hospital stay have resulted from CT use, conferees said. In metastatic brain tumors, CT identifies and localizes single and multiple lesions earlier than previous techniques, thus permitting optimal treatment of both the metastatic and primary lesions. The conference found CT the most useful diagnostic study for a number of other intracranial disorders and that there are no absolute contraindications to its use. . . . **ANTHONY MILLER**, member of the Board of Scientific Counselors of NCI's Div. of Resources, Centers & Community Activities: "I can't imagine a community physician, let alone a community oncologist, spearheading prevention activities. Practicing physicians deal with active disease." Responded fellow Board member **CHARLES MOERTEL**: "If you want any prevention program, you will have to go to the community center oncologist. You can't get others involved without him. If you get him involved from scratch, he'll go, and you've got everyone else."

DRCCA BOARD GIVES CONCEPT APPROVAL TO STUDY ON BLACK-WHITE DIFFERENCES

(Continued from page 1)

The subcommittee agreed that an RFA should be offered "which will allow investigators to develop ideas, and see what they come up with," Greenwald said. A second recommendation was that a chemoprevention office be established in DRCCA with appropriate staff, and that DRCCA undertake some studies with that staff. "That will take some time," Greenwald said.

"I'm very supportive of the concept of chemoprevention," said Board member Ernst Wynder. Suggesting that epidemiologists and chemists should be encouraged to work together, Wynder said, "The Sporns of the world (referring to Michael Sporn who heads the Laboratory of Chemoprevention in the Div. of Cancer Cause & Prevention) work better when they are put into the same room." Leads which might be followed up in human trials, Wynder said, include dietary fiber, vitamin C, consumption of green and yellow vegetables, and zinc. "Whitmore found years ago that prostatic cancer tissue is low in zinc. I'm amazed no one has picked that up."

"Chemoprevention is beginning to build up public steam," Carter said. "If we've learned anything, it's not to let the public get ahead of the data."

Board member Anthony Miller said there is a need for more epidemiology work, "But I wouldn't hold up going ahead with trials." Answers may never be available unless some interventions are tested "with carefully identified groups in carefully designed trials," Miller said. "We can run into incredible ethical problems We may have a terrible time getting people to agree to double blind studies."

"I don't think it is sufficient to throw epidemiologists and chemists together," Eagle commented. "We need some bridge work, and I haven't seen evidence that it exists. I saw one study, and was shocked at the lack of sophistication in the dose schedule."

Wynder said that studies should include both initiators and promoters. The fact that Japanese emigrants to the U.S. experience an increase in colon cancer in the first generation indicates it is related to promoters. Breast cancer does not decline until the second generation, and that indicates it has to do with an initiator, Wynder said. "It is important that we try (studies) relating low dietary fat to breast cancer incidence," Wynder said.

Carter noted that "all epidemiological studies are associated with vegetables. There are many things in vegetables besides vitamins, antioxidants for one. How far down can you get in dietary history to dissect out facts other than vegetables yes, vegetables no. There could be 15 different things interacting."

"The important effect from vegetables is fiber," Miller said.

"If you eat a lot of vegetables, by definition you eat less meat and fats," Wynder said.

"Studies involving thousands of people can be terribly expensive," Board member Charles Moertel cautioned. "Once they are done, they are considered the be all and end all. Dose variations are important, and our knowledge is rudimendary. We might hit a home run, but the chance is great that we won't. I hope the RFA will take this into consideration."

"We should be aware of what is going on in industry," Carter said. "It would be a tragedy to put out an RFA and then find out that Hoffmann LaRoche is already doing it."

NCI would like to fund some chemoprevention clinical trials in the 1982 fiscal year. To do so, a deadline for receipt of applications will have to be established early enough to permit review before the May meeting of the National Cancer Advisory Board.

In other actions, the Board:

• Approved the concept of a study of the survival differences between black and white cancer patients. At least one contract at an estimated $100,000 a year for three years would be awarded competitively, and possibly one more. The staff narrative describing the project:

For many years data on cancer mortality have indicated a definite survival gap between blacks and whites for patients with cancer at various body sites. Blacks show a poorer prognosis for most types of cancer, even when adjustments have been made for age and stage of disease. Among both sexes the racial difference is particularly large for cancer of the colon, rectum, urinary bladder, and Hodgkin's disease. Among women alone, the survival rates for breast cancer and cancer of the uterine corpus are much lower for blacks than whites, and among men there are large racial differences for cancer of the larynx, prostate, and kidney.

A growing awareness of the scope of this problem has prompted a call for research aimed at identifying causes of the survival differences and mechanisms for reducing the racial gap. In February 1981 the National Cancer Advisory Board made a commitment to try to remedy the poor survival experience of black cancer patients. Using available data on cancer incidence and mortality, some preliminary hypotheses can be developed concerning the possible causes of racial differences in survival. However, further research is required to evaluate the relative importance of contributing factors.

These factors might include: differences in demographic characteristics which are not adjusted for in estimating relative survival rates (e.g., inequalities in socioeconomic status); differences in histology of the tumors involved; differences in the stage of disease at diagnosis within gross categories such as localized disease; differences in host vulnerability to the growth and spread of cancer; differences in concomitant diseases that might hasten death from cancer; differences in patterns of treatment; and differences in biological and behavioral responses to treatment, including disparities in compliance.

Behavioral processes may impact on the racial difference by influencing promptness of consultation and the stage of disease at diagnosis. Social factors may also affect utilization of the medical system for the treatment of cancer and host vulnerability to its recurrence and spread. Since differences in survival rates between black and white cancer patients show considerable variation by site of disease, the investigator

should select a target population in which such disparities have been established. Attention should then be directed toward explaining these differences. Regardless of the explanatory approach, it will be necessary to determine how much of the racial variation in survival is due to differences in the extent of disease at diagnosis.

The investigator should go beyond gross designations of stage such as localized, regional, or remote disease and determine as precisely as possible the size of the lesion and the degree of metastasis. Once this task has been completed, the investigator should attempt to ascertain how much of the survival advantage for whites remains to be explained. Assuming that significant survival differences persist for whites and blacks when adjustments have been made for the extent of disease at diagnosis, it is recommended that the applicant pursue one or more lines of further inquiry as suggested above: histology, host vulnerability, demographic attributes of the patients, treatment patterns, and/or treatment compliance.

• Approved the concept of funding longterm followup of a population which participated in controlled trials of colorectal cancer screening using an occult blood test, but only after slashing the amount of money proposed.

The project was started in 1974 by the National Large Bowel Cancer Project, one of the four organ site programs. The screening has been largely completed, and it will be necessary to follow about 22,000 persons for six more years. Staff had proposed that this be accomplished through a noncompetitive contract with Strang Clinic and Memorial *Sloan-Kettering* Cancer Center, where the screening was done, at a cost ranging from $300,000 in the final year to $640,000 a year.

Andrew Chiarodo, chief of the Organ Sites Branch, told the Board that the Large Bowel Cancer Project could not fund the followup because it would not have any money left after honoring ongoing commitments.

Moertel and Board member Charles Cobau objected to the cost estimate, contending that followup should be substantially less. Miller agreed, and proposed that it be limited to $200,000 a year maximum after the first year (FY 1982) in which a total of $500,000 would be required to complete the screening and initiate the followup. The Board agreed, but there was no consensus on whether the funds should come through the Organ Sites Program or through a contract.

Carter suggested members express their preferences on the mechanism in letters to Greenwald, and that process is still going on.

Moertel objected to "the idea of taking a project funded and approved by the organ site mechanism and then finding the investigator needs more money, and rather than move money from within the program, asks for it from the general budget. The Organ Site Program is already in a favorable position. This approach is carrying favoritism too far."

• Disapproved the concept of a noncompetitive contract with Baylor College of Medicine, Massachusetts General Hospital, Mayo Clinic, and Univ. of Southern California to continue funding the DES-adenosis Project carried out by the four institutions at a cost of $700-800,000 a year.

The project has enrolled more than 5,000 women in the study of effects of in utero exposure to DES. The study has found, contrary to earlier fears, that squamous neoplasia does not occur more frequently in exposed women. The project was proposed for continuation to "test specific hypotheses relating to the continuing risk of genital tract neoplasia following DES exposure; investigate further major health issues relevant to the DES exposed population; and identify and elucidate those aspects of the DESAD Project experiences which are applicable to research and practice for cancer in general."

"This problem has passed from the research mode to the public health domain," Cobau said. "Every gynecologist worth his salt knows about it. This would take $3.5 million of our budget. Are we not beating to death something we already know?"

Greenwald said former division Acting Director William Terry had advised the group to submit a grant application, and it had done so. "The choice here is, do we do this noncompetitively, or let them take their chances with the grant?"

The Board took the latter option.

• Deferred to a new Subcommittee on Occupational Cancer a proposal for an RFA to develop strategies to increase worker awareness of exposure to carcinogens and modify protective behavior in the workplace. Four grants at an estimated cost of $80,000 a year each for three years would be funded.

The proposal would include screening, identification of risk factors, and education of workers.

"We should delete screening," Miller said. "This is not a screening program."

"I would put my money on changing the smoking habits of asbestos workers," Wynder said. "That would have the most impact."

"I abhor the use of respirators as a means of reducing risk," Board member Kaye Kilburn said. "That's like wearing a necklace. A better answer would be to provide a sucker to pull the bad air out of the workplace and bring good air in."

Carter suggested that concerns of the Board should be addressed by staff and the subcommittee. Norbert Roberts was named by Carter as chairman of the subcommittee, which includes Kilburn, Leonard Derogatis, and Doris Wilkinson.

• Approved the report of the Ad Hoc Subcommittee on Cancer Centers which considered a suggestion by NCI Director Vincent DeVita that a better method than core grant support might be found to support nonclinical (laboratory) cancer centers. The subcommittee's conclusion:

"It is the strongly held view of this subcommittee that laboratory cancer centers should continue to be

considered as 'cancer centers' under the purview of DRCCA, and eligible for core grant support. Most of the 18 centers which would be affected by this proposal are qualitativaely and quantitatively in the forefront of cancer research. The major dislocation and disruption of those programs resulting from the proposal to eliminate that core support would seriously and adversely affect the individual centers as well as the total national cancer research effort. Many of these centers could not continue to function were the crucial support now provided by the core grant no longer available."

DeVita also had asked the Board to consider the question of geographic dispersion of centers. The subcommittee reported:

"Because of limitation of time, the subcommittee dealt only briefly with the question of the number and geogrpahic dispersion of cancer centers, i.e., whether there should be a specific optimal target number of centers, whether the concentration of centers in the northeast, for example, was an undesirable development, and whether there should be an effort to disperse centers more widely than is now the case.

"To the first point, those at the meeting were unanimous in the view that there should not be a specific target number, but that the determinant should be the quality of the individual application. From the perspective of scientific quality, particularly in the basic sciences, the density of cancer centers would not appear to be a relevant issue. The only important issue would be the quality of the science at the centers, and not whether there were other centers in the same geographic area. There was not, however, extensive discussion of the fact that an increase in the number of approved centers in the face of a constant budget would necessarily result in decreased average budgets per center.

"From the perspective of clinical research, however, density could be a relevant issue. Clinical research requires patients with specific diseases, in several stages. If the density of centers within a region became too great, competition would develop for clinical research resources (patients) which could diminish cost effectiveness and impinge upon the implementation of the research program. Thus, it is apparent that the density of centers would have to be related to the population of cancer patients within the area who could be entered into research protocols.

"A third perspective would be that of cancer control research. If cancer control research is to be largely geared to a defined population base, then the proliferation within a small area of centers interested in such studies would be detrimental, unless optimally coordinated.

"In summary, the regional density of cancer centers may be a relevant issue for optimal conduct of clinical and cancer control research cancer centers. It is not considered to be an important or determinant issue in the evaluation of basic research centers."

NEW PUBLICATIONS

"Accomplishments in Cancer Research 1980," edited by Joseph Fortner and Jonathan Rhoads. Second in a series by the General Motors Cancer Research Foundation. Includes presentations by each of the laureates of the 1980 Cancer Research Awards made by the Foundation—Elwood Jensen, Elizabeth and James Miller, and Isaac Berenblum. J.B. Lippincott Co. (price not available).

"Sarcomas of Soft Tissue and Bone in Childhood," an NCI monograph. Proceedings of the symposium held in Orlando in 1979, sponsored by the Cancer Clinical Investigation Review Committee. For sale only by Supt. of Documents, U.S. Government Printing Office, Washington D.C. 20402. Contact that office for price and ordering information.

"The Prostatic Cell: Structure and Function," edited by Gerald Murphy, Avery Sandberg, and James Karr. A comprehensive two volume multidisciplinary examination from both clinical and basic perspectives. Alan R. Liss Inc., 150 Fifth Ave., New York 10011. Part A, "Morphologic, Secretory, and Biochemical Aspects," is $80 per copy; Part B, "Prolactin, Carcinogenesis, and Clinical Aspects," $60.

RADIATION ONCOLOGIST OBJECTS TO ACR CLAIMS COMPARING RESULTS TO SURGERY

Manuel Vider, chief of radiation oncology at the Univ. of Tennessee Center for the Health Sciences, took exception to comments by Luther Brady, Gerald Hanks and Morris Wizenberg in an American College of Radiology seminar (***The Cancer Letter,*** Oct. 2). ACR presented data which it contended demonstrate that radiation therapy is equal to or better than surgery in treating some malignancies. In a letter to the editor, Vider wrote:

"I am obliged to reply to. . .what I believe is a narrow view by Brady, Hanks and Wizenberg.

"The report, if it accurately translates the thought of the presentors, tries to convey that there is a confrontation between radiotherapy and surgery in the treatment of early breast cancer. They mention little or nothing of the later stages and have no mention of the brachytherapy techniques.

"The Veronessi[1] report is good, maybe very accurate, but the panel of the ACR fails to mention that it actually selects the favorable population since the study was limited to disease under 2 cm in diameter.

"The Pierquin[2] technique has a similar approach, which was followed by Hellman and Levene[3]. It is unfortunate that the ACR panel didn't mention the brachytherapy techniques emphasizing stages 0 and 1; and less the stages 2 and over. The use of brachytherapy is not intended and limited to these stages

but is also applied with increasing success in all stages, (T_3, T_4 and inflammatory carcinomas) by Syed[4] and his group and Wasserman et al[5].

"In the limited experience in our center we have the same impression as that of the latter reports. I would like to repeat that the kind of radiotherapy that we practice is actually getting closer to the surgical team, using surgical techniques and participating in a team work with equal footing for the brachytherapist and surgeon.

"Whether we want it or not, the medical centers contain a large number of sub-specialties. It is impractical and even damaging to try to confront one with another, claiming better results than others. In fact, what the patient wants is the best treatment through the best team without quarreling between doctors.

"Personally, I don't consider myself represented by the ideas put forward in that report."

(1) Veronessi, U., et al.: Comparing Radical Mastectomy with Quadrantectomy, axillary diss. and radiother. in patients with small cancers of the breast. N. Engl. J., Med. 305: 6-11, 1981.

(2) Pierquin, B., et al.: Radical radiother. of breast ca. Int. Radiother. Oncol. Biol. Phys. 6:17-24, 1980.

(3) Hellman, S., et al.: Radiation ther. of early ca. of the breast without mastectomy. Cancer 46: 988-994, 1980.

(4) Syed, A.M. Niser, et al.: Combination of exter. and interstitial irrad. in the primary management of breast ca. Cancer 46: 1360-1365, 1980.

(5) Wasserman, T.H., Sickles, G.A. and Phillips, T.L.: Primary radiation treatment of colloid carcinoma of the breast. Cancer 48: 1972-5, 1981.

GARB CALLS FOR COMBINING PHASE 1, 2, ABOLISHING DRG, CUT INDIRECT COSTS

Solomon Garb, clinical professor of medicine at the Univ. of Colorado, clinical pharmacologist involved in treating cancer patients and developing new chemotherapy regimens, chairman of the Citizens Committee for the Conquest of Cancer which helped to bring about the National Cancer Act of 1971, and now a cancer patient himself, could not be expected to stay on the sidelines in the controvery over anticancer drug development.

Garb wrote a statement which he submitted to the House Health Subcommittee to be included in the record of the joint Waxman/Gore hearing on drug development. Garb addressed much of the criticism leveled at NCI in the *Washington Post* articles, added a few critical points of his own, and offered some suggestions for improvements. Excerpts follow:

Is the informed consent procedure now used by NCI adequate?

It is as adequate as human ingenuity can make it. The problem is not in the informed consent form or in what the doctor tells the patient, but in what the patient understands or is willing to understand. I don't think that the informed consent procedure is a serious problem.

What is the adequacy of animal testing prior to exposing humans to experimental drugs?

Unfortunately animal tests are inherently inaccurate in predicting human toxicity. Most animals metabolize drugs differently than people do. The monkey is one of the poorest predictors of drug toxicity in people. Monkeys may look like people, and may act like people but monkeys do not resemble people in their metabolism of drugs or reaction to drugs. Of the animals used generally in drug studies, the mouse is as good as any in predicting human toxicity, but it isn't as good as we wish. Also, there is little to gain from extensive long term toxicity studies of anticancer drugs in dogs, and a lot to lose in terms of cost, time, and patients' lives. If we are limited to the usual experimental animals, I'd have to say that our present procedures are as good as we are likely to get.

If we used other species of animals, we might get additional useful information. Studies with a variety of drugs (but not anticancer drugs) have shown that the domestic pig is quite similar to people in its metabolic patterns and its response to drugs. To my knowledge, no one has ever done a thorough study of the value of pigs in predicting toxicity of anticancer drugs in people. I would like to see moderate contracts to several veterinary schools to explore thoroughly the use of pigs in drug toxicity studies, not only for anticancer drugs, but for a wide variety of drugs.

Why do experimental clinical protocols permit the continued testing of drugs that are found to be severely toxic in humans?

In the history of medicine, drugs that were severely toxic in initial studies were found to be much less toxic when changes were made in the dosage, timing of administration, route of administration, or adjuvant drug therapy. This pattern has been repeated with the anticancer drugs. Cisplatin was initially so toxic to the kidneys that it was considered useless for clinical treatment. However, a fairly simple adjuvant treatment to protect the kidneys, using mannitol, made cisplatin a useful and reasonably safe drug. It has already saved the lives of thousands of patients with cancers of the urogenital system, and will save tens of thousands more in the next few years.

What potential is there for conflict of interest in clinical researchers between their responsibility to patients and the requirements of the experimental protocols?

That depends entirely on the phase of the clinical studies. Phase 2, 3, and 4 studies have a negligible potential for such conflict of interest because the legally specified intent of such studies as defined by the FDA is evaluation of therapeutic benefit to the patient, and of course, the physician's primary responsibility to the patient is to provide maximum therapeutic benefit. The situation is entirely different with phase 1 studies. Here, the potential for conflict of interest between the physician's responsibility to the patient and the requirements of the protocol is close to 100 percent. The reason is that the primary purpose of a phase 1 study as mandated by FDA is evaluation of a drug's toxicity and clinical pharmacology. Production and evaluation of therapeutic benefit is only a secondary purpose. The physician's primary responsibility to the patient, however, is production of maximum therapeutic benefit, so a conflict of interest is virtually inevitable.

I hasten to add that this situation is in no way the fault of the National Cancer Institute or the clinical investigators. They are forced into it by FDA regulations. Nor is the situation the fault of any of the current FDA officials. FDA regulations concerning phase 1 studies were developed years ago, before the pitfalls were clearly understood. Today's FDA officials, as government officers, have no choice but to follow and enforce the regulations. . . .

For most types of drugs, the FDA regulations on phase 1 studies work quite well. Phase 1 studies on new sleeping medications, headache remedies, antibiotics, diuretics, and so forth are done on normal healthy volunteers who are paid a fee for their services. To my knowledge, no healthy volunteer for

phase 1 studies on these kinds of drugs has ever died or suffered serious injury.

Unfortunately, when the new drugs have a high level of inherent toxicity, the situation is reversed. Almost all anticancer drugs are intrinsically toxic and cannot ethically or legally be tested in normal, healthy volunteers. They must be tested in patients suffering from the disease in question, and generally, are tested in patients with advanced disease who cannot be helped further with standard treatments. This inevitably leads to the serious conflict of interest described above. It also leads to all kinds of other problems, since the patient with advanced disease is less able than a health volunteer or patient with early disease to withstand any kind of toxicity.

The higher level of FDA officials are well aware of this situation, and over the years, the wording of FDA regulations on phase 1 studies has been softened. Some of the earlier versions stated flatly that the primary purpose of phase 1 studies was evaluation of toxicity. The most recent official version of FDA guidelines available to me, that of September 1977, mentions studies of clinical effectiveness, but relegates that to a secondary role.

Fortunately, senior, responsible FDA officials are aware of this problem and are trying to rectify it. The Concept Document, Investigational and New Drug Regulations—Revisions, of October 1979, suggests a much more acceptable and humane definition of phase 1 studies. . . .

Can anything be done to speed necessary reforms? In 1971, the U.S. Senate Panel of Consultants on the Conquest of Cancer was aware of the developing conflicts of interest involved in phase 1 studies, and we therefore proposed a solution which would have been quite suitable for that time. Our recommendation suggested that a National Cancer Authority have "The power to authorize exceptions to existing regulations, where necessary, to permit the use of experimental drugs, biologicals, and devices in cancer research."

Unfortunately, we did not document the need for such a change adequately and it was not adopted. Today, it might be possible to achieve the same goal by a simpler method.

I respectfully suggest that this committee take the leadership in sponsoring a joint resolution of Congress, stating, "It is the intent of the Congress that all clinical studies involving patients with a disease should be so designed that the primary purpose is to provide the maximum possible therapeutic benefit to the patients." I am confident that because of the high regard in which this committee is held, such a resolution would be adopted by an overwhelming margin. It would not only eliminate the conflict of interest in current phase 1 studies, it would encourage and facilitate the combination of phase 1 and 2 studies. This in turn would help all patients, would speed the development of newer, less toxic drugs, would increase cost effectiveness, and would strengthen the hands of the responsible senior FDA officials who are trying to help patients.

Does the National Cancer Institute turn down innovative grant requests from investigators who are not members of an inner circle?

The answer is a categorical no. The National Cancer Institute does not and cannot turn down any investigator-initiated requests for R01 grants. These are the grant requests that are the main subjects of current controversy and television programs. The decision to approve or disapprove a grant request is made by the Div. of Research Grants of the National Institutes of Health, the higher administrative body. DRG (with its advisory committees doing peer review) approves or disapproves applications for R01 grants for all the institutes in NIH, not just NCI. If DRG disapproves a grant, no one—not the director of NCI, not the secretary of HHS, not even the President of the United States can reverse the decision.

By NIH regulation, the letters to grant applicants informing them that their grant applications have been disapproved are sent by the individual institutes. Thus an applicant for a disapproved cancer research grant receives a letter from NCI notifying him of the disapproval. NIH does not permit that letter to point out that the disapproval came from DRG. It is not therefore surprising that most disapproved cancer grant applicants assume they were turned down by the Cancer Institute.

When a grant application is approved but given a priority too low for funding, that is also done by DRG which assigns priority scores. The director of NCI has only minimal flexibility in deciding whether to adhere to the DRG priority scores. The same is true, of course, for other institutes.

When my good friend Dr. Joseph Gold, and the Nobel laureates whom I greatly admire, Drs. Albert Szent-Gyorgy and Linus Pauling were notified that their R01 grant applications were disapproved, they naturally assumed that NCI had done it and became highly critical of that institute and its leadership. That criticism led to all sorts of unfavorable publicity for NCI, all of it unfair and undeserved. The target of the criticism should have been DRG.

Does DRG, nevertheless, follow NCI wishes and guidelines in evaluating R01 grant applications? No. In at least two areas that I know of—Cancer and Nutrition and Cancer Causation—DRG and its advisory committees went against the publicly expressed wishes of the NCI director, the National Cancer Advisory Board, and Congress in disapproving a large series of grant applications.

Does DRG appoint to its advisory groups those scientists whom the NCI director recommends? Rarely. It usually ignores such recommendations, so they are seldom, if ever, made now.

Let us now rephrase the question. Does the Div. of Research Grants of NIH turn down innovative grant requests from investigators who are not members of an inner circle? My answer is yes, and frequently. Of course, this applies to all the institutes, not just cancer.

What can be done? My suggestion is that DRG be abolished and that each institute be given the authority and responsibility to approve, disapprove and give priority scores to grant applicants in their fields. If they have to take the heat, they should have the decision making power. Applications that are not clearly in the area of a particular categorical Institute can be sent initially to the Institute of General Medical Sciences.

Is the current "peer review" system fair and equitable or does it discriminate against innovative ideas from scientists who are not members of the "research establishment"?

The current system, as organized and maintained by DRG, is not fair or equitable and frequently discriminates against innovative ideas. This, of course, applies to all medical research, not just cancer. However, the current system is not a true "peer review" system. A true peer review system would be one in which the reviewers are elected by the people under review, or selected by a random process like a jury. Also, in a fair peer review system, the reviewers must not have any vested interest in the outcome. A potential juror who was a known competitor of a defendant, or on the other hand, a close friend of a defendant or litigant, would be automatically disqualified by the judge from serving on that jury. By contrast, in the present DRG system for evaluating grant requests, almost all the jurors are competitors of the applicant, some are close friends, and some are scientific adversaries. The only regularly enforced reason for disqualifying a study section member is that he is currently at the same institution as the applicant.

What can be done to correct this? The problem is complex, without simple solutions. I hope Congress will schedule full hearings on the "peer review" system soon, to explore ways

of making it more responsive to the nation's needs and to American concepts of fairness. There are two steps that I would recommend. One, as mentioned earlier, is abolition of DRG and reassignment of its mission to the individual institutes within NIH. The second is a sharp reduction in the present excessive and exhorbitant indirect cost (overhead) rates to some universities and institutions where the research is carried out. In addition to saving hundreds of millions of taxpayer dollars, this would reduce the fierce competitive pressures on scientists to bring in funds and allow them to concentrate on research to help patients.

Does NCI accept suggestions from outside scientists for changes and improvements in its testing procedures?

Yes. In the past six years, I have made several suggestions to NCI for major changes in their animal testing and screening procedures. Three were put into effect before 1980, and I have just been informed that a fourth suggestion has been accepted and incorporated into their new procedures. Of course, my suggestions were presented in scientifically valid form, supported by thorough documentation, and in some cases by pilot studies that I and my associates carried out. Not all my suggestions have been adopted, but all were considered fairly and carefully. Those of my suggestions that were accepted were not all adopted as rapidly as I would have liked, but then, I tend, to be a bit impatient. As a government agency, NCI must follow standardized procedures, and they take time. From what I can determine their speed in making necessary changes and improvements compares favorably with that of other government agencies.

Do NCI and the American Cancer Society try to discourage trials of newer, less conventional treatments?

A recent national television program (20/20) implied that NCI and ACS tried to discourage such trials, and gave two examples, one of them hydrazine sulfate. The television reporter then concluded by saying that FDA (presumably in contrast to NCI and ACS) felt there was enough merit in hydrazine sulfate to authorize three cancer centers to start clinical trials on it.

The first authorization for such trials was issued to me after approval by FDA on March 25, 1980, of my IND, No. 16,274 in which I am both sponsor and principal investigator. The second and third authorizations were issued by FDA to UCLA (Harbor Hospital) and to the Bowman Gray School of Medicine in North Carolina. Both of their protocols are almost identical to mine, since they cross-filed my protocol with my written approval and permission. Surely, I would be the one to know the most about any NCI or ACS opposition to these studies, but the television reporter never bothered to contact me and the television program came as quite a surprise.

The facts are exactly opposite from the impression given by the television program. When I was preparing my protocol, I submitted it, as required by federal regulations, to the Institutional Review Board of the institution in which I planned to do the study. A physician on the staff objected vigorously to any studies on hydrazine sulfate, and the IRB deferred its decision. I wrote to both ACS and NCI asking their positions. Their replies were similar. Both stated that they welcomed well-designed, controlled, carefully conducted clinical studies to settle the question of hydrazine sulfate's value, and both encouraged me to go ahead. I presented these letters to the hospital IRB and they then approved my request.

Not only did NCI and ACS not try to block the hydrazine sulfate studies, their letters of support were crucial in getting IRB approval. Had it not been for their fairness and objectivity in this matter, there would be no hydrazine sulfate clinical studies under way in this nation at all. Both NCI and ACS deserve praise, not blame. I guess the lesson is that one ought not take seriously dramatic television exposes.

There is a related issue that I would like to call to the attention of this committee. I have received many requests from physicians around the nation to use on their patients investigational drugs for which I had an approved protocol. Hydrazine sulfate is one example, but there are others. Some of the requests came from physicians who did not have the background or training to use investigational drugs safely in cancer patients, and I would not have granted their requests in any event. Some of the requests, however, came from highly qualified physicians with worldwide reputations whose qualifications I consider equal or superior to mine. Unfortunately the cross-filing procedure, which is laborious and complicated, would have taken so much time that their patients would have died before the drug was available.

In the past, there was a procedure that enabled a qualified physician to use an investigational drug to help a particular patient without undertaking a formal, expensive, clinical trial on many patients. That procedure was called a "compassionate IND." It seems to have been changed or made more difficult to obtain—at least it was denied to the eminent physicians who wanted to use some of the drugs for which I was principal investigator. Accordingly I hope this committee will consider sponsoring a joint congressional resolution expressing congressional intent that the compassionate IND be reinstated for use by qualified physicians in individual patients.

Cancer is the most complicated and dreaded of the diseases that afflict large numbers of people. It is exceedingly frustrating to deal with, whether one is a patient, physician, nurse, scientist, or government official. We must guard against letting our frustrations affect our judgment, particularly in blaming people or groups for less than ideal progress. Despite the insinuations, half-truths, and misleading statements in certain newspapers, the only real villain is cancer itself. We must work together to conquer it, and not squabble among ourselves.

NCI and ACS are doing superior jobs and deserve great credit for approximately 40,000 to 60,000 extra American lives that will be saved this year because of improved diagnosis and treatment developed and improved since 1971. The senior, responsible FDA officials, faced with the difficult task of reconciling 1963 regulations with 1981 clinical realities are doing a fine job in trying to reduce needless delays and red tape. The FDA officers of all ranks whom I have dealt with have been uniformly fair, cooperative, and helpful, although at times their hands were tied by obsolete regulations. Physicians and nurses around the nation have made excellent, and at times, unexpected progress in preventing or reducing undesirable side effects from cancer treatment and cancer itself.

Above all, the United States Congress, representing all the people of the United States, deserves the highest possible praise from the world and from future generations for its initiation of the National Cancer Program in 1971, and for its continuing support of that program. Knowing this nation's leadership in the worldwide fight against cancer, and knowing that we will save many thousands of extra lives this year, makes me particularly proud to be an American and to have helped advance this great goal in my own small way. On behalf of myself and other cancer patients, I want to express our appreciation to this committee, and to this and past congresses for your support of the National Cancer Program.

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR DECEMBER, JANUARY

National Cancer Advisory Board—Dec. 1-2, NIH Bldg. 1 Wilson Hall, second and third days of annual program review, 8:30 a.m., open.

President's Cancer Panel—Dec. 3, International Club, Washington D.C., 9 a.m., open.

Tumor Cell Heterogeneity: Biologic & Clinical Implications—Dec. 3-4, Johns Hopkins Medical Institutions, Turner Auditorium, Baltimore. Fourth Annual Bristol-Myers Symposium on Cancer Research. Contact Ellie Trowbridge, Symposium Coordinator, Rm 169, Johns Hopkins Oncology Center, 600 N. Wolfe St., Baltimore 21205, phone 301-955-2583.

Large Bowel Cancer Review Committee—Dec. 7, Eden Roc Hotel, Miami Beach, open 8:30–9 a.m.

National Conference on Gastrointestinal Cancer—Dec. 8-10, Miami Beach, Fontainebleau Hilton. Sponsored by the American Cancer Society, with Paul Sherlock, Memorial Sloan-Kettering Cancer Center as chairman. Sessions are scheduled on risk factors, management planning, treatment, and diagnosis. Stephen Carter, director of the Northern California Cancer Program, will present a special lecture on future directions in therapy. Contact ACS, National Conference on GI Cancer, 777 Third Ave., New York 10017.

Bladder Cancer Review Committee—Dec. 10-11, Logan Airport Hilton, Boston, open Dec. 10, 8:30 a.m.–noon.

Current Concepts in Cancer Therapy—Dec. 10-12, St. Louis. Sponsored by Washington Univ. and the American Cancer Society. Contact Office of Continuing Medical Education, Box 8063, 660 S. Euclid Ave., St. Louis 63110, phone 304-454-3873.

Human Interferon—Dec. 10, Roswell Park continuing education in oncology. Contact Gayle Bersani, Cancer Control Office, RPMI, 666 Elm St., Buffalo, N.Y. 14263.

Clinical Cancer Program Project Review Committee—Dec. 14-16, Bethesda Marriott Hotel, open Dec. 14, 8:30–10 a.m.

Histocompatibility Antigens and Cancer—Dec. 14, Paris. Contact J. Levy, Hopital Cochin, 27, rue Fg St. Jacques, 75014 Paris.

3rd Conference on Human Tumor Cloning—Jan. 10-12, Univ. of Arizona Cancer Center, Tucson. Optional primer course Jan. 10, invited and competitively selected papers Jan. 11-12. Sydney Salmon and Jeffrey Trent are cochairmen. Contact Mary Humphrey, Conference Coordinator, Univ. of Arizona Cancer Center, Tucson 85724, phone 602-626-6044.

From Gene to Protein: Translation into Biotechnology—Jan. 11-15, Konover Hotel, Miami Beach. 14th Miami Winter Symposium sponsored by Univ. of Miami and Papanicolaou Cancer Research Institute. Frontier areas of genetic experimentation, including translation of lab processes into practical applications. Contact Miami Winter Symposium, P.O. Box 016129, Miami 33101, phone Sandra Black, 305-547-6265.

Gynecologic Oncology Group—Jan. 14-16, Omni Hotel, Miami. Business meeting. Contact John Kellner, Group Manager, GOG Headquarters, 1234 Market St., Suite 430, Philadelphia 19107, phone 215-854-0770.

NCI Div. of Resources, Centers & Community Activities Board of Scientific Counselors—Jan. 14-15, NIH Bldg 31 Rm 4, 8:30 a.m. both days, open.

Breast Cancer Task Force—Jan. 19-20, NIH Bldg 31 Rm 6, 8:30 a.m. both days, open.

Assn. of American Cancer Institutes—Jan. 24-26, UCLA Jonsson Comprehensive Cancer Center, semiannual meeting.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

RFP NCI-CM-27517

Title: *Synthesis of congeners and pro drugs*
Deadline: *Approximately Feb. 1, 1982*

The Drug Synthesis & Chemistry Branch of the Developmental Therapeutics Program of NCI's Div. of Cancer Treatment is seeking contractors with chemical synthesis expertise to synthesize a variety of compounds for evaluation as potential anticancer agents.

The objectives of this project are: (a) to synthesize congeners of synthetic compounds with confirmed activity; (b) to design and synthesize "pro drugs" and other compounds that possess elements of both congener and "pro drug"; (c) to synthesize compounds related to products of natural origin and other related heterocycles.

It is anticipated that two 3½ year projects will be initiated with a level of effort of approximately three staff years per year each.

Contracting Officer: John Palmieri
RCB, Blair Bldg. Rm. 228
301-427-8737

RFP NCI-CO-23901-41

Title: *Technical writing, publications distribution, and telephone answering services in response to cancer related inquiries*
Deadline: *Jan. 18, 1982*

NCI is soliciting proposals for a small business firm to provide communications services to support the Office of Cancer Communications.

This proposed procurement is a total set-aside for small business concerns. A small business, for purposes of this procurement, is a firm, including its affiliates, that is independently owned and operated, is not dominant in the field of operations in which it is bidding on government contracts, and has 500 employees or less (FPR 1-1.701.1 (a) (2)).

This project is for a three year period. Offerors will be limited to those firms having operating facilities within a 35 mile radius of Bethesda, Md. as daily person to person contact is often necessary.

Contract Specialist: Diane Smith
RCB, Blair Bldg. Rm. 332
301-427-8745

The Cancer Letter _Editor Jerry D. Boyd

Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.