THE CANCER LETTER

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SENATE SUBCOMMITTEE OKAYS $1 BILLION FOR NCI IN FY 1980, AGREES TO BLOCK OBEY REPROGRAMMING

A determined, eloquent effort by Sen. Birch Bayh resulted in approval of an appropriation of $1 billion for NCI by the Senate HEW Appropriations Subcommittee, although Bayh and Sen. Richard Schweiker failed to get an overall increase for NIH over the amount

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In Brief

ACCIDENTS CLAIM WISCONSIN'S WILLIAM CALDWELL, JOHN WEAR; MURCHISON, NANCE TO HEAD NALSI

TRAGEDY HAS hit the Univ. of Wisconsin School of Medicine faculty two more times. William Caldwell, associate director of the Wisconsin Clinical Cancer Center and director of the Div. of Radiation Oncology, died while on vacation in Canada of carbon monoxide poisoning due to a faulty propane appliance in a cabin in which he, his wife and a cousin were staying. The cousin also died, but Mrs. Caldwell, also stricken, is recovering. Caldwell, 49, was chairman of the NCI Clinical Cancer Program Project Review Committee. John Wear Jr., professor and chairman of the section of urology in the Dept. of Surgery, died in the DC-10 crash in Chicago. Anthony Curreri, who died in early May of apparent cardiac arrest, had served as the first president of the Uniformed Services Univ. of Health Sciences in Bethesda, from 1974 to 1977, before returning to his faculty position at Wisconsin. . . . **HOWARD ULFELDER**, director of Massachusetts General Hospital's Cox Cancer Center and president of the ACS Massachusetts Div., received the 1979 Lucy Wortham James Clinical Research Award from the Society of Surgical Oncology. . . . **JANE TAYLOR**, chief of NCI's Breast Cancer Program Coordinating Branch, was chosen Woman of the Year by the Breast Diseases Assn. of America. . . . **THOMAS MURCHISON**, president of Dawson Research Corp., is the new chairman of the board of directors of the National Assn. of Life Science Industries. He replaces Donald Nielsen, president of Hazleton Laboratories of America. James Nance, president of Litton Bionetics, is president of NALSI; Donald MacArthur, president of Enviro Control, and John Landon, president of EG&G Mason Research, are vice presidents; Gilbert Maton, president of Tracor Jitco, is treasurer; and John Kolojeski, president of Clement Associates, is secretary. . . . **VITAMIN A DEFICIENCY** increases the risk of bladder cancer, Curtis Mettlin, Roswell Park senior researcher in the Dept. of Biological Resources, told members of the Society of Epidemiological Research this week. Mettlin reviewed questionnaires seeking information on dietary habits of 1,600 patients admitted to RP between 1957-65. Foods measured for intake quantities included vitamin A rich sources such as carrots, milk, fruit and tomatoes. Persons reporting the lowest levels of vitamin A intake carried a risk of bladder cancer twice that of persons reporting the highest level, Mettlin said.

BAYH, SCHWEIKER LEAD FIGHT FOR MORE MONEY FOR NIH, BUT MAGNUSON PREVAILS

(Continued from page 1)

voted by the House Appropriations Committee for the 1980 fiscal year.

The Senate subcommittee's total for NIH, in fact, is $56 million less than the House figure of $3.381 billion, one of the rare times the subcommittee has not added substantially to House totals for biomedical research.

Bayh, Indiana Democrat, first tried to get what he said was a simple 8% cost of living increase for NCI, the National Heart, Lung & Blood Institute, the National Institute of Arthritis, Metabolism & Digestive Diseases, and the National Institute of Neurological & Communicative Diseases & Stroke. "Those are the areas where the most people are dying and are being crippled," Bayh said. That would have put NCI's total at 1.03 billion.

Bayh's amendment was defeated 8-6, with Subcommittee Chairman Warren Magnuson (D.-Wash.), Lawton Chiles (D.-Fla.), Quentin Burdick (D.-N.D.), Thomas Eagleton (D.-Mo.), Daniel Inouye (D.-Hawaii), and William Proxmire (D.-Wisc.) voting against it. Magnuson also cast negative proxy votes for subcommittee members not present—Robert Byrd (D.-W.Va.), and Ernest Hollings (D.-S.C.).

All of the Republicans on the subcommittee voted for the Bayh amendment—Richard Schweiker (Pa.), Mark Hatfield (Ore.), Charles Mathias (Md.), Harrison Schmitt (N.M.) and Lowell Weicker (Conn.).

Magnuson, who has backed away from his previous all out support of NIH since he became chairman of the parent Appropriations Committee, had proposed an increase of $153 million over the President's budget request for NIH of $3.172 billion. Schweiker offered a substitute motion, adding $60.8 million to the House figure, which would have been about $117 million more than Magnuson was requesting.

The Schweiker motion was defeated by the same lineup that sank the Bayh proposal.

It was not clear in either the Magnuson or Schweiker proposals what the individual institute totals would be. Magnuson explained only that the increases over the President's budget would be used to fund grants down to the 210 priority scores. Schweiker argued that while the President's budget would have cut the number of competing new grants which could be funded by 46%, Magnuson's proposal would reduce that only to 20%. Schweiker said his plan would fund the same number of competing grants as is being funded in FY 1979.

After Bayh lost out with his proposal to get additional funds for the four institutes, he agreed to support Schweiker's plan provided Schweiker would agree to specify that NCI's appropriation would be $1 billion. Schweiker went along with that, to no avail when his motion was defeated.

Bayh was not ready to give up. Winding up more than an hour of arguing with Magnuson and Proxmire, Bayh offered another amendment to the Magnuson motion, putting NCI's appropriation at $1 billion. Magnuson, who earlier had indicated he would go along with the higher figure for NCI in Bayh's first motion if Bayh would drop the increases for the other three institutes (Bayh did not agree), said, "There's no need to argue about this any longer. To save time, the chair will accept that amendment."

Just how the balance of the $153 million will be apportioned to the institutes may have to wait until the committee report is written. The increase to $1 billion for NCI would require $63 million.

The Senate committee report also will have something to say about the effort by Congressman David Obey to reprogram $17 million from Cancer Control and construction to the Toxicology Program (***The Cancer Letter***, June 1).

"May I also ask that in the language of the report, we undo what Obey is trying to do?" Bayh asked. "He took several million out of community cancer control programs, which we need to apply the benefits of research, and put it in the search for carcinogens. I think there probably is already enough money in that program, but if we do need more, let's appropriate more for it and not take it out of the community programs."

Schmitt also was alarmed by the Obey maneuver. "Let's make it clear in the report that the intent of the committee is that there will be no reduction in community cancer control programs, that money will not be transferred out to the Toxicology Program," Schmitt said. "I would like to additionally urge NCI to make every effort to stimulate community outreach, and community based cancer control programs."

The House Appropriations Committee, which approved $961 million for NCI, specified in its report that $18.2 million of the $24 million increase over the President's budget would be for new and competing renewals of investigator initiated research grants. The report also said the "Committee believes that an increase of $23 million is justified to get the National Toxicology Program fully under way as quickly as possible. It has therefore included a $6 million increase in the NCI appropriation and directs that an additional $17 million be reprogrammed, from the $84.6 million included in the budget estimates for cancer control and construction, to the National Toxicology Program.

"The reprogramming of cancer control funds shall, however, effect no reduction of funds for activities aimed at educating the public or preventing the occurrence of occupational or environmentally caused cancer. It is expected that the additional $23 million for the National Toxicology Program will make it possible to test 100 new compounds."

By exempting prevention and education programs

from the cancer control cuts, Obey limited the reductions primarily to NCI's community programs. Those amount to about $42 million of the Div. of Cancer Control & Rehabilitation's $65 million budget.

The construction budget for 1980 is $15 million, with $10 million for grants and $5 million for contracts. The construction contracts are all for the Frederick Cancer Research Center and NCI's share of the addition being built to the NIH Clinical Center.

NCI executives, considering the impact of Obey's action, lean toward taking $5 million of the cut from construction and $12 million from control, if they are forced to comply with the House report. No consideration has yet been given to how that would be split between FCRC and grants (the amount for the Clinical Center is committed).

Taking $12 million from the $42 million which supports community programs, cancer control grants, rehabilitation grants, pain research, cancer center core grants and all the other programs which are not considered prevention or education would be a major blow to some of those efforts. It most certainly would mean that no new programs could be started; it probably would mean that some existing contracts and grants would have to be phased out one or two years ahead of schedule, with all the disruption and waste that would entail.

The action by the Senate subcommittee this week could save the situation, if the full committee and the Senate agree and the Senate prevails in the conference with the House.

As for the total budget, the Senate action could mean that NCI will wind up with $980 million, if the usual 50-50 split of the difference occurs in conference. It now appears more than likely that NCI will be able to fund 40-45% of new and competing renewal grants.

Part of the dialogue between Bayh and Magnuson involved increased support for interferon research and development. Magnuson said his amendment called for $30 million to be allocated to interferon. Bayh agreed to that in getting Magnuson to go along with the $1 billion.

Bayh opened his fight by saying, "As strongly as I feel, I don't want to suggest that I'm more interested in saving lives than anyone here. The fact is, if you look at the budget, there is not a single area where we can continue make the progress we are making today. . . .

"There are thousands of people alive today because of the advances we have made in cancer. Some of us have not been fortunate enough to win that battle (Bayh's wife, Marvella, died earlier this year of breast cancer), but that doesn't mean we shouldn't continue trying."

After citing progress in other areas, especially the reduction in mortality from heart disease, Bayh continued, "To say we're going to fight inflation on the backs of those with epilepsy, MS, cancer, a whole list of diseases we're still fighting, is not acceptable. This is not the time to fight inflation by backing away from health. When you've got the ball on your opponent's five yard line, that is not the time to punt. We're making great progress in cancer research, and this is not the time to punt."

Schweiker argued strongly for stability in supporting research grants. "If you want good researchers to stay in the business, you've got to provide stable support. We can do that with just $60 million more than the House figure for NIH."

Schmitt, a new member of the subcommittee this year, argued that the best way to fight inflation is to reduce the cost of health care, and to do that, "we've got to produce cures. It is inconceivable that a President going around the country crowing about all the support he's giving to basic research will propose a budget that will reduce biomedical research by 46%."

Proxmire, unmoved, offered a motion to hold NIH to the President's request. He cast the only vote for it.

TOTAL MASTECTOMY PLUS NODE DISSECTION 'SATISFACTORY ALTERNATIVE,' PANEL SAYS

"Total mastectomy with axillary node dissection can be considered a satisfactory alternative to the Halsted radical mastectomy and (can be considered) the current treatment standard for stage 1 and selected stage 2 breast cancers."

That was the "consensus" reached by panel members on the Conference on Treatment of Primary Breast Cancer: Management of Local Disease," sponsored by NCI's Div. of Cancer Treatment and the NIH Office of Medical Applications of Research.

The panel members also reached consensus on two other points:

- Diagnostic biopsy separated from definitive therapy is the procedure of choice in the majority of breast cancer cases, permitting patients to participate in treatment decisions.
- Routine use of radiotherapy after mastectomy is a moot point which can't be addressed until further results are in from adjuvant chemotherapy trials. If chemotherapy delays or prevents recurrence, radiotherapy may not be needed, the panel agreed.

The panel noted that "trials with primary radiotherapy and segmental mastectomy with radiotherapy are yielding exciting preliminary results and warrant further support from both patients and physicians."

Panel members were John Moxley, conference chairman, vice chancellor of health sciences at the Univ. of California (San Diego); Franco Muggia, director of NCI's Cancer Therapy Evaluation Program; Jane Henney, special assistant for clinical affairs in DCT; Joseph Allegra, of DCT's Clinical Investigation Branch; John Durant, director of the Univ. of Alabama Comprehensive Cancer Center; Rose Kushner, executive director of the Breast Cancer Advisory

Center, Kensington, Md.; Jerome Urban, Dept. of Surgery, Memorial Sloan Kettering Cancer Center; Bernard Fisher, Univ. of Pittsburgh and chairman of the National Surgical Adjuvant Breast Project; Umberto Veronesi, National Cancer Institute of Milan; Samuel Hellman, director of the Joint Center for Radiation Therapy, Harvard; and Jacques Pierquin, Dept of Radiotherapy, Henri Mondor Univ. Hospital Center, France.

Urban offered the only defense of the radical mastectomy, contending that "adequate primary surgery" is necessary to achieve local control, and "adequate" often demands radical surgery.

But Fisher, Veronesi, Hellman and Pierquin all presented data from trials they have conducted which indicate no advantages as far as local control is concerned for radical mastectomy over total mastectomy plus radiation, segmental mastectomy, segmental mastectomy plus radiation, tumor excision plus radiation.

Panel members discussed at some length the "multicentricity" of breast cancer. They agreed that Veronesi's data indicate "tissue remaining after surgery (in his segmental trials) harbors no clinically significant breast cancer. Nevertheless, the clinical significance of the multifocal nature of breast cancer needs further study."

FDA COMMITTEE OKAYS TWO NDAs, NIXES ONE, HEARS NCI TOXICOLOGY PROPOSAL

The FDA Oncologic Drugs Advisory Committee recommended approval of two new drug applications for anticancer agents and disapproval of another at the committee's meeting last week. The committee also heard presentations on the status of clinical investigations with thymidine; received a terse communication from FDA Commissioner Donald Kennedy which reversed a policy the committee had established more than two years ago regarding criteria for an NDA approval; heard FDA staff announce it will attempt again to develop guidelines for clinical testing of antineoplastic drugs; and received the proposal by NCI's Div. of Cancer Treatment for changing the preclinical toxicology protocol, which would drop for the most part requirements for using large animals.

Committee recommendations on NDAs are not binding on FDA. The final decision is made by the staff, in the commissioner's name, but the staff generally goes along with advisory committee recommendations.

The committee recommended approval of dacarbazine (DTIC–Miles) for second line treatment of Hodgkin's disease in combination with other effective agents (declining to specify which agents) and for treatment of soft tissue sarcoma in combination with adriamycin.

Robert Benjamin, M.D. Anderson; Joseph Bertino, Yale; and Emil Frei, Sidney Farber, reported on studies with DTIC as a single agent and in combination for treating sarcomas and Hodgkin's disease. Frei said the results indicate that used with adriamycin, bleomycin, and vincristine, DTIC "certainly is at least as good as MOPP" in treating advanced HD. He also noted that a study by Gianni Bonadonna in Italy in which ABVD was used in a cycling regimen with MOPP shows somewhat better results than MOPP alone.

Frei also said that while MOPP patients are at a four fold increase in risk over the normal population for developing AML (20-30 times higher if MOPP is used with radiotherapy), "when comparing patient years, ABVD produces no increased risk of AML."

The committee agreed with member Stanley Balcerzak that "the case is well made for DTIC as an active agent in treating both soft tissue sarcomas and Hodgkin's disease, although significantly less for sarcomas." The vote to approve the NDA for HD was unanimous.

Committee member Charles Haskell expressed reservations about the agent's effectiveness is sarcomas. "It is difficult to evaluate for sarcomas," he said. "The data strongly suggest some benefit when added to combinations. I would feel better if we had long term results. I can't convince myself that DTIC and adriamycin is better than adriamycin alone."

Benjamin, who reported on the Southwest Oncology Group's DTIC studies, said they were analyzed to determine if any factors could have contributed to differences, other than DTIC. "There were none . . . . The SWOG studies involved hundreds of patients in a number of institutions. Results were duplicated. The historical controls were valid." Although the differences were small, "small differences become very big when hundreds of patients are involved."

The motion to approve DTIC for treatment of soft tissue sarcoma in combination with adriamycin was approved 7-2, with Haskell and Carol Portlock casting the negative votes.

A motion requiring the package insert to specify that combinations containing DTIC should be used as second line therapy for Hodgkin's disease was approved 6-3, with Balcerzak, John Whitaker and Jack White opposing it.

The committee recommended approval of hydroxyurea (Hydrea–Squibb) in combination with radiotherapy for treating head and neck tumors.

George Richards, Greater Baltimore Medical Center reported on 2,000 patients with advanced head and neck cancer who were treated with hydroxyurea and radiotherapy, in many cases prior to surgery. Tumor reduction was substantial, Richards said, often permitting tumors first considered inoperable to be removed "with local surgery as the definitive therapy." Ten year survival is 58%, Richards said.

Committee Chairman Philip Schein pointed out that two other trials did not find that hydroxyurea contributed to improvement. Committee member Brigid Leventhal agreed. "I would say we need an-

other good trial," she said.

The proposed package insert states that the agent is a radiosensitizer, but Leventhal said, "We have no evidence to support that. Not that it doesn't have clinical results. There is no test that shows hydroxyurea alone is ineffective. It may be effective alone, and what we have is a combination radiotherapy-chemotherapy effect."

White suggested that action be deferred until further data is available, but a Squibb representative asked "for more definitive action. This has been dragging on for some time." The motion to approve was carried unanimously.

The committee refused to recommend approval of the NDA for estramustine (Emcyt–Hoffmann-La Roche) for treatment of prostatic cancer. Data presented by Arnold Mittelman on a study at Roswell Park, and by Ralph Benson on a Univ. of Wisconsin study, failed to convince committee members of the compound's efficacy. Committee member Leon Hellman raised questions about its mechanism of action and contended that its benefit may be that of an alagesic derived from its estrogen component.

Schein suggested that survival evidence was "soft," although FDA statisticians felt that evidence pointed to improved survival for patients receiving estramustine.

Balcerzak argued that "I think we've seen enough evidence that this agent is active," and cast the only vote against the motion to oppose approval of the NDA.

Robert S.K. Young, group leader for oncology drugs, presented the committee with a statement from Commissioner Kennedy which was a response to the committee's disapproval in 1976 of an NDA for methyl CCNU as treatment for colorectal cancer.

Charles Moertel, who was a committee member then, argued that although MeCCNU produced measurable responses, it had not improved survival. The committee went along with Moertel on a split vote, rejecting established policy that anticancer drugs could be approved for marketing on the basis basis of evidence of response without considering survival data.

Representatives of Bristol, the drug's sponsor, bitterly argued that this was changing the rules in the middle of the game, to no avail.

Kennedy was not commissioner at that time (and he will soon leave for a position at Stanford–no successor has yet been announced). His statement, read by Young, was succinct:

"A sufficient measure of effectiveness for purposes of approval of an NDA is response rate data alone. Other data such as data on survival are not absolutely required."

DCT Director Vincent DeVita presented NCI's proposal for changing preclinical toxicology guidelines, which would eliminate entirely use of subhuman primates and also, for the most part, eliminate use of other large animals. Under the new guidelines, initial toxicological studies would be based on the mouse.

The proposal:

Since the inception of the Drug Development Program (formerly Cancer Chemotherapy National Service Center) at NCI in 1955, guidelines for toxicologic studies have existed. They have routinely employed single and multiple dose treatments primarily in mice, rats, dogs and monkeys. While the protocol published in 1964 emphasized the dog and monkey, the most recent procedures include both of the large animal species and the mouse. This latter species was added to evaluate it as a potential replacement for the large animal species.

Since studies under the existing toxicology protocol take about nine months to complete at a cost of approximately $100,000-$120,000 per compound, NCI proposes here a revised preclinical toxicology protocol for antineoplastic agents to facilitate introduction of new anticancer drugs to the clinic.

Several important considerations impinge on the proposed revisions. First, before a drug can advance from phase I to phase II clinical trials, a formal affirmative Decision Network (DN 4) vote must be obtained from the DCT 30-member DN committee. Thus, in the past the philosophy was to conduct animal toxicologic studies for phase II trials and beyond. Under the new proposal, some options might stipulate , for example, that only if unusual toxicities occur during phase I would more detailed animal studies be considered before phase II trials indicate some efficacy and therefore the likelihood of wider use in a variety of patients.

Another point related to the one above involves the important concept of defining the number of individuals "at risk" from the potential hazards of being treated with a drug not extensively studied. About 100 individuals are at initial risk in the average phase I trial. This is not very different when compared with some other classes of phase I drugs. The patient population under study is unique. The likelihood of survival without effective treatment is low.

We propose that initial toxicological studied be based on the mouse alone (Option A). In selecting this option, the initial clinical dose would be based on 1/10 the mouse LD_{10} value rather than 1/3 LD_{10} to provide a greater margin of safety. Lack of toxicity would be expected for greater than 90% of the oncolytic agents. For drugs in this category, we would proceed with phase I studies using the dose doubling escalation procedure. If toxicity were observed the modified Fibonacci procedure would then be used for dose escalation. Upon completion of phase I clinical trials, results are presented to the DCT DN committee at DN 4 where approval is sought to proceed with phase II clinical trials. Following completion of phase II trials in the signal tumors, if efficacy is demonstrated against any human tumor, the drug can either be assigned to Group C, with FDA approval, or designated as a candidate for an NDA or both. In either case, should it be determined that histopathologic or chronic toxicity studies are required, such studies would be initiated in the dog or mouse at this point in the development of the drug to expedite its introduction into medical practice. The nature of these studies is uncertain, especially as to schedule or chronicity which should probably reflect the clinical usage at the time.

Option B is an alternative and less preferred proposal which would combine use of the mouse and dog for initial quantitative toxicology studies. However, limited qualitative toxicologic data would be obtained in that hematology and clinical chemistries would be obtained for both species. Gross pathologic changes would be recorded at time of necropsy and tissues taken at this time would be preserved for later histopathologic evaluation. It should be noted that a dose response effect would be sought in the dog, but the four defined doses stipu-

lated by the currently used protocol would no longer be required. Note that selection of the initial clinical dose using this option is based on the most sensitive species, either 1/3 LD_{10} in the mouse (rather than 1/10 LD_{10}) or 1/3 TDL in the dog. Development of the drug would proceed as in Option A except that tissues from both species would be available for histopathologic studies where required prior to NDA submission as an alternative to or in addition to other toxicology studies started at that time.

(NCI estimated that Option A—using the mouse only—would cost $12,400 per compound if histopathologic evaluation is excluded, $15,500 if it is included. Time required would be 1-2 months without the pathology, 2-3 with. Under Option B, the cost would be $56,400 without pathology, $66,500 with, and time required 2-3 months without, 3-4 months with).

These estimates have been revised to take into account recent information regarding actual cost of our studies. Both protocols will not only reduce the time required for these studies from nine months to about four months, but will also reduce costs substantially, particularly with Option A, and thereby make it feasible for research groups outside of the DCT to conduct toxicology studies required for their own INDAs.

The major strengths of these suggested protocol revisions stem from the following information: Firstly, questions were raised as to the real need of including the monkey in such studies. Through a combination of a fresh look at some old data and in updating the Schein report of 1970, there appears no longer to be sufficient justification for inclusion of this species in routine protocol studies. On May 11, 1979, following a presentation by the DCT at the FDA, it was agreed by all parties present to terminate the use of monkeys for preclinical toxicology studies.

Secondly, newly acquired data is available on quantitative toxicity animal-human correlations. The latter correlations are based on a toxicity ratio (TR) value defined as the ratio of the maximum tolerated human dose to 1/3 LD dose in the mouse or 1/3 the toxic dose low (TDL) in the dog where doses for all species are expressed on the mg/square meter (mg/sq m) basis. These toxicity ratios as used by Goldsmith, Slavik and Carter and Gottlieb have been similarly calculated for a variety of drugs and schedules.

Fifty-five drug schedules have been analyzed; this is more than twice the number analyzed in any previous studies. Using the mouse alone with a starting dose in the clinic set at 1/3 the LD_{10} dose, there is an approximate 20% risk of severe toxicity and for the dog a 9% risk factor (TR less than 1) during phase I trials. Thus, combining data from both species and selecting the starting dose from the more sensitive species eliminated the risk factor for this group of drugs and schedules. However, when 1/10 the LD_{10} dose in the mouse is used the risk is essentially eliminated and furthermore the potentially dangerous toxicity for compounds with a TR less than 1 when analyzed carefully is minimal by current clinical standards. It should also be noted that there is very little difference in the number of escalation steps using the doubling method and 1/10 the LD_{10} (a median number of 4 steps) when compared with the more traditional Fibonacci method using 1/3 the mouse LD_{10} (a median number of 3 steps).

A retrospective analysis was done to determine whether a dose equivalent to or greater than 1/3 the mouse LD_{10} (mg/sq m) had been used in the clinic for drugs listed in (a table accompanying the statement). Even though the starting clinical dose was based on 1/3 the LD_{10} rather than 1/10 the LD_{10}, only camptothecin gave drug related lethalities as reported by Moertel. Another drug, porfiromycin, was not given near the MTD predicted from mice. Since it did not cause significant marrow depression at 22 mg/sq m, it can only be speculated as to how severe toxicity would be at 90 mg/sq m. For most of the drugs, marrow toxicity was the dose-limiting toxicity. Certainly with the current supportive technology available, this kind of toxicity is much more manageable than was experienced during phase I trials conducted for some of the more established antineoplastic agents.

NCI is soliciting comment from the scientific community on its proposal. Write to Vincent Oliverio, Associate Director, Experimental Therapeutics Program, DCT, NCI, Bethesda, Md. 20014.

Schein appointed a subcommittee consisting of Valerie Mike, Haskell, Hellman and himself to study the proposal. The subcommittee will reports its recommendation conclusions at the committee's next meeting, Oct. 11-12.

Both NCI and the Oncologic Drugs Advisory Committee have resisted FDA attempts to adopt clinical testing guidelines.

FDA tried in 1976 to write guidelines acceptable to the committee and to NCI, but failed. A year later, FDA submitted a draft of proposed guidelines for testing anticancer drug combinations, but the committee rejected it.

Young told the committee last week that the 1976 draft would be resubmitted for its consideration. Vincent Bono, chief of DCT's Investigational Drugs Branch, said "the issue is the need for guidelines." He cited these points:

- FDA already has written and published general guidelines which apply to all drugs (the agency also has adopted specific guidelines for most drug classes, with anticancer drugs a notable exception).
- NCI has fostered guidelines for its contractors and grantees, and institutions where clinical trials are conducted are required to establish certain standards.
- A joint US-USSR monograph on drug development includes guidelines for clinical testing and is available.
- DCT is currently developing policies for more effectively insuring that in evaluation of an investigational agent, studies to serve as a basis for an NDA application are appropriately conducted.

"Since investigators applying for an IND have access to existing guidelines, there is no need for additional ones," Bono said.

Mike, Portlock, Schein, Whitaker and Moertel, who is no longer a committee member but is retained as a consultant, were named to a subcommittee to develop a recommendation on the guidelines.

Some committee members, concerned that national publicity about thymidine had resulting in rushing the drug into phase 1 trials before preclinical tests had been completed, asked for a review of the trials and toxicology work.

DeVita inferred that some of the criticism was aimed at the validity of DCT's drug screening program. "If you use a system that only predicts based on drugs we already have, we will be forever locked into those types of drugs that are cytotoxic, bone marrow suppressive and cause hair loss," he said. "We operate under the maxim that when nothing prevails

SCHMIDT SAYS HE ERRED IN REMARKS ABOUT LINUS PAULING'S APPLICATIONS

Benno Schmidt, chairman of the President's Cancer Panel, commented during a discussion at the meeting of the National Cancer Advisory Board last September on the efforts by Linus Pauling to get NCI support for some of his research. Schmidt's comment on Pauling followed his observation that one reason why nutrition research had not been better supported by NIH was because "grant applications didn't come in that could pass peer review."

Board member Bruce Ames pointed out that Nobel Prize winner Pauling was one who had not succeeded in getting a grant for research with vitamins. Schmidt responded:

"His application really wasn't a grant application. It was a request for funds. He wrote describing some research with vitamins in England and said if he had $300,000 he could do some good work in that area. He was asked if he would put his request in the form of an application, and he said that he couldn't."

Those remarks were published in ***The Cancer Letter.*** Schmidt acknowledges now that he was misinformed.

"In ***The Cancer Letter*** of Sept. 22, 1978, I am quoted as saying at a recent meeting of the National Cancer Advisory Board that Dr. Linus Pauling's applications to do research with vitamins as a possible tool in cancer treatment and prevention were not 'really grant applications, but rather were a request for funds.'

"This statement was in error and I would like to correct the error. The fact is that Dr. Pauling has submitted five research grant applications since 1973. Each of these was submitted in the proper format and accepted by the Div. of Research Grants for review. Two of the grants received study section approval but were given priority scores too low for funding. Three other applications were recommended for disapproval primarily because of the lack of essential details, documentation, and adequate controls.

"My statement that Dr. Pauling's applications were 'not grant applications' was an erroneous interpretation on my part of information which I had been given verbally to the effect that Dr. Pauling's poor priority scores and disapprovals stemmed from the absence in his applications of essential details, documentation, and controls.

"I regret any inference that Dr. Pauling attempted to operate outside normal grant application channels."

GERTRUDE, WERNER HENLE TO RECEIVE $25,000 BRISTOL-MYERS RESEARCH AWARD

Gertrude and Werner Henle will receive the second annual Bristol-Myers Award for Distinguished Achievement in Cancer Research. The $25,000 cash prize will be presented at a luncheon in New York April 9.

The Henles are members of the research staff of the Joseph Stokes Jr. Research Institute at Children's Hospital of Philadelphia and professors of virology in pediatrics at the Univ. of Pennsylvania Medical School.

Since coming to the U.S. from Germany more than 40 years ago, the Henles have concentrated their research on virology and immunology. They became interested in viral oncology in the early 1960s.

"The Henles showed that the Epstein-Barr virus, a previously unknown human virus, is the cause of infectious mononucleosis and involved in the development of two human cancers, Burkitt's lymphoma and nasopharyngeal carcinoma," said John Ultmann, director of the Univ. of Chicago's Cancer Research Center and chairman of the panel that selected the Henles for the award.

"These discoveries," he said, "are the basis for research on how the presence of a viral nucleic acid in the nucleus of a cell can turn a normal cell into a malignant one. Once we understand this change, we may also learn how non-viral cancers are induced."

Klaus Hummeler, director of the Stokes Research Institute, who nominated the husband-wife team, said, "The Henles began their cancer research with a single idea—that if there is a virus, there must be antibodies to fight it. When they found large concentrations of antibodies to the Epstein-Barr virus in patients with two human tumors, they established the first cause and effect relationship between a virus and human cancer."

Winners of the Bristol-Myers award were selected by a five member panel of judges from cancer research centers at Baylor, Chicago, Johns Hopkins, Stanford and Yale universities. Each of those universities participates in a $2.5 million grant program funded by Bristol-Myers.

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the contract officer or specialist named, NCI Research Contracts Branch, the appropriate section, as follows:

Biology & Diagnosis Section and Viral Oncology & Field Studies Section—Landow Building, Bethesda, Md. 20014; Control & Rehabilitation Section, Carcinogenesis Section, Treatment Section, Office of the Director Section—Blair Building, Silver Spring, Md. 20910.

Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NO1-CO-95460-04

Title: *NCP management information system support services (programming)*

Deadline: *Approximately May 20*

(The proposed procurement is 100% set aside for small business concerns.)

NCI is soliciting proposals to provide technical support services to the Office of the Director in the expansion, maintenance, and operation of NCI's Management Information System. MIS consists of a series of user managed subsystems which have been designed to meet the information needs of various line and staff organizations while at the same time providing data which can be aggregated to provide summary information to the Office of the Director.

Maintenance support will provide modification of computer programs, testing, installation, user training, and documentation updates for software and/or procedural changes approved by the MIS Configuration Control Board. Operations support will be used primarily to initialize systems at the start of a new fiscal year and to operate, test or prototype systems prior to release to the user.

For these activities, the contractor will provide personnel experienced in the use of an operating environment similar to that of the NIH Div. of Computer Research & Technology. The implementation support will provide software and related documentation based on MIS/PO-prepared specifications.

Activities in this category would be similar to and would require similar skills to those provided under maintenance support. Offerors shall be limited to those firms having operation facilities within one hour's commuting time of the NIH campus as continued interaction between the contractor and the MIS staff is often necessary.

Contracting Officer: D.M. Keefer
Office of Director
301-427-7984

RFP NO1-CO-95456-10

Title: *Short training course for biosafety officers on the practices and procedures for the control of biohazards in the research laboratory*

Deadline: *May 17*

NCI intends to issue an RFP to obtain the services of an organization capable of giving detailed instruction to institutional biosafety officers on the day-to-day tasks of biohazard control such as hood certification, air monitoring, emergency procedures, decontamination of spills and decontamination of a laboratory.

In addition, instruction would be given on how to organize, plan, develop and conduct a laboratory safety program to deal with the biohazard safety problems associated with research organisms containing recombinant DNA molecules, infectious agents, oncogenic viruses and chemical carcinogens.

Contract Specialist: Kris Boyer
Office of Director
301-427-7984

RFP NO1-CP-95616

Title: *Rodent disease diagnostic laboratory*

Deadline: *May 21*

The objective of this project is to provide diagnostic laboratory support by conducting quality assurance examinations of animals produced for, and used by the Carcinogenesis Testing Program. Complete examinations will consist of gross necropsy examinations, histologic preparation of tissues, microscopic diagnosis, recording and tabulation of lesions.

In addition, microbiological culturing and serum collection for rodent virus serology profiles will be performed routinely. The study should be designed to interpret and determine any significance of findings to assure that disease problems are minimized by monitoring the health status of rodent colonies.

Contract Specialist: Ursula Evans
Carcinogenesis
301-427-7914

RFP NO1-CP-95617-59

Title: *Rodent production colonies*

Deadline: *May 21*

The objective of this project is to establish rodent production colonies to produce rats and mice. The colonies will be cesarean derived, barrier maintained, and tested to assure the absence of pathogenic contaminates.

The pedigreed axemic nucleus colony will be housed in germfree isolators and will be the source of breeders for the flora-associated expansion colony, which will also be housed in germfree isolators. The production colony will be housed in a barrier maintained room.

At intervals, pedigreed litters will be received from the Genetics Unit, NIH, to rederive the nucleus colony and maintain genetic homogeneity with the NIH strains. The proposer will provide rats and mice of equal sex distribution on a weekly basis to users designated by official NCI personnel.

Contract Specialist: Roland Castle
Carcinogenesis
301-427-7914

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