THE CANCER LETTER

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P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

House Appropriations Adds $20 Mil. To Bush Request For NCI, Emphasizes Three Cancers

The House Appropriations Committee added $20 million to the President's FY 1992 budget request for NCI, a relatively small increase compared to previous years, but representing 40 percent of the $50 million the committee added to the President's request for NIH.

(Continued to page 2)

In Brief

Olden Chosen To Head NIEHS; Cancer Panel To Discuss Cancer And Poverty On July 9

KENNETH OLDEN, director of the Howard Univ. Cancer Center in Washington, was chosen to head the National Institute for Environmental Health Sciences and was sworn in last week. NIEHS has been without an official director since David Rall retired last September. Olden has no background in environmental research, but is an excellent basic scientist and manager, sources said. He will give up his voting seat on the National Cancer Advisory Board, but will be an ex officio member as NIEHS director. . . . **PRESIDENT'S CANCER PANEL** will meet July 9 at NIH Bldg. 1, Wilson Hall, from 8:30 a.m.-noon. HHS Secretary **Louis Sullivan,** NIH Director **Bernadine Healy,** and NCI Director **Samuel Broder** are among the speakers scheduled to address the issue of cancer and poverty. The meeting is open. . . . **PHONE NUMBER** for Robert Clark, Assn. of Community Cancer Centers president-elect, was incorrect in the May 31 issue of **The Cancer Letter.** The correct number is 217/788-3000. Clark is the contact for those interested in a forthcoming request for proposals for the management of ACCC. . . . **EDWARD BRESNICK** ended his term as chairman of the Div. of Cancer Prevention & Control Board of Scientific Counselors. Other members rotating off the board were **James Gaylor** and **James Holland.** . . . **"PREVENTION ISN'T SEXY,"** complains Maryann Roper, former NCI deputy director, now a consultant to the Carter Center of Emory Univ. and a member of the Div. of Cancer Prevention & Control Board of Scientific Counselors. "But prevention is what is going to affect the bottom line in cancer incidence," Roper said in a discussion of future prevention initiatives. "Everyone who parades through Washington wants to see [NCI Surgery Branch Chief] Steve Rosenberg's lab. Everyone wants to touch the gene. Diet isn't sexy. No one wants to touch a pear." . . . **CORRECTION: The Cancer Letter's** May 31 issue incorrectly described the bylaws revision passed by ASCO members at their recent annual meeting. The revision states that one director will be chosen from "two candidates, who are from specialties other than medical oncology or hematology."

House Adds $20 M, Emphasizes Breast, Ovarian, Prostate Cancer

(Continued from page 1)

Cancer program advocates said last week they were disappointed that new budget constraints imposed by three-year deficit reduction measures enacted last fall severely limited the amount of money the Appropriations Committee could add to the President's request. However, the advocates said the fact that the committee did give NCI the largest percentage of the added amount represents an acknowledgement of NCI substantial budget needs.

The appropriations bill, reported out of committee last week, includes $1.830 billion for NCI, an increase of $116.7 million over the Institute's FY91 operating level of $1.714 billion, or a 6.8 percent increase.

The committee said it arrived at that figure after taking $17 million in reductions "as a result of a generally policy of reallocating indirect cost savings, freezing unauthorized activities at the 1991 level and blocking transfers to the Agency for Health Care Policy & Research." These reductions were then offset by an increase of $38 million for high priority needs. Of this amount, $30 million is to be used for "increased attention" to breast, ovarian, and prostate cancer.

In addition to those amounts, the committee said it expects NCI "to redirect resources within its base appropriation to these devastating cancers." The remaining increase, the committee said, "will permit expansions of existing programs of research in the areas of vaccine development, proton beam therapy, and pediatric AIDS drug development."

The total NIH appropriation in the House bill is $8.824 billion, $50 million above the President's request and $548 million above the FY91 operating level, for a 6.6 percent increase. Following are the areas the committee identified for priority in NCI:

Women's health–The committee urges NCI to increase its commitment to women's health through all its components, particularly clinical trials. The Institute is expected to play a major role in the design and implementation of the trans-NIH Healthy Women Study that will address the causes, treatment and prevention of diseases most responsible for morbidity and mortality in women such as cancer, cardiovascular disease, and osteoporosis. While some progress has been made against certain cancers which affect women under 65 years of age, additional efforts are needed to improve the cancer statistics for women over 65, poor women, and women from certain minority groups.

Breast cancer–Breast cancer is expected to claim over 45,000 women's lives this year. One in nine women will be diagnosed with the disease in her lifetime. Yet there has been little progress in finding the cause or cure for this disease. The committee considers additional work in this area one of the highest priorities of the National Institutes of Health. NCI has several initiatives underway with regard to the problem of breast cancer. NCI will establish a "Specialized Program of Research Excellence" using the center grant mechanism to provide research funds for fully integrated laboratory-clinical investigation of breast cancer and rapid translation of basic scientific discoveries into clinical application. The program requires a major institutional commitment on the part of the grantee center receiving the award by stressing developmental funds to support pilot interdisciplinary collaborative projects as well as career development. NCI will explore the potential of restricting fat intake to lower the risk of developing breast, colorectal, and possibly other cancers as well as cardiovascular disease through a three year feasibility study to assess methods for achieving dietary change among minority and less educated women as well as for non-minority participants. A larger dietary fat research study will also be coordinated as part of the trans-NIH Health Women Study. A second randomized clinical trial is scheduled to begin later this year to assess the tumor suppressive effects of tamoxifen in women at high risk for developing breast cancer.

Ovarian cancer–More than 12,000 women die each year of ovarian cancer, and over 20,000 are diagnosed with the disease, usually in the late and least survivable stages. The committee expects NCI to more aggressively pursue research in this area. To address the issue of ovarian cancer in women over the age of 65, NCI will join with the National Institute on Aging to sponsor a conference entitled, "Perspectives on Ovarian Cancer in Older Women: Current Knowledge and Recommendations for Research." NCI will initiate a large scale trial designed to determine whether screening with a pelvic examination along with the use of antibody CA 125 and transvaginal ultrasound in females ages 60-74 can reduce mortality from ovarian cancer. Other studies are examining the relationships between obesity, endocrine and fat metabolism and increased risk of ovarian, breast and uterine cancers in postmenopausal women.

Prostate cancer–The incidence rates of prostate cancer are increasing each year, and are expected to continue to rise in proportion to the increasing life expectancies of American men.

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Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

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Cancer and poverty–The committee urges the Institute to continue its efforts to reach disadvantaged populations, to educate them about the importance of prevention and the need for early diagnosis and timely treatment.

Cancer prevention and control–The committee urges NCI to continue to emphasize the importance of cancer prevention and control research and recognizes the key role of the Community Clinical Oncology Programs in these efforts. The CCOP network of community cancer specialists, primary care physicians, and other health care professionals represents a critical component in NCI's clinical trial network. The Minority-Based CCOPs reach out to minority populations and provide disadvantaged groups with access to state of the art therapy through clinical trials as well as cancer prevention and control research. The committee expects that CCOPs will be maintained at least at 1991 funding levels.

The committee also urged NCI to "more aggressively pursue international collaboration in cancer prevention, with special emphasis on training and information dissemination."

The report also asked NCI to "explore the impact on survival and quality of life from psychosocial counseling services as part of the medical care offered," and to undertake a demonstration study on payment mechanisms for psychosocial services in cancer centers.

Clinical trials–The committee encourages the Institute to continue to explore alternative means to disseminate important new research results derived from clinical trials to reduce the long delays that sometimes accompany the publication of scientific results in major peer reviewed journals.

Proton beam therapy–The committee has, over the past two years, funded a program to plan for several dedicated state of the art hospital based proton research and treatment facilities which could serve as a regional center for continuing research and application of this promising therapy. From the hearings and the report received from the Institute it appears that the planning phases have reached a satisfactory stage of completion. Thus, the committee has provided $4 million for the initial phase of construction and procurement of equipment for from one to two such region proton therapy centers, a process which is anticipated to extent for an additional two or three years. The committee expects these funds to be awarded to those centers which received planning funds in 1991 through the established NCI peer review process.

Vaccine development–The committee notes the new prospects for cancer vaccines and urges NCI to explore and develop innovative approaches for such vaccines. The Institute is encouraged to use the full breadth of molecular biology, immunology, tumor biology, and its clinical trials apparatus to bring about testable vaccines as rapidly as possible. Further, the Institute is urged to facilitate the general transfer of knowledge from the laboratory to the bedside, and to maintain flexibility in the funding mechanisms used for this purpose. The committee continues to have great interest in this area of research and directs NCI to use funds from the increase provided to strengthen its efforts in this area.

The committee understands that NCI is considering reducing program project grants in an effort to increase the overall number of awards. The committee is concerned about this policy and urges the Institute to consider the issue carefully.

The committee also mentioned the joint NCI-National Heart, Lung & Blood Institute studies of gene therapy.

FDA Crackdown On Off Label Use Information Anti-Intellectual: Chabner

The Food & Drug Administration's crackdown on Bristol-Myers Squibb for allegedly promoting off label uses of several of the company's anticancer drugs has added a new dimension to the on again, off again battle between the agency and NCI.

FDA contends that several publications produced or sponsored by Bristol promoted off label uses of carboplatin, cisplatin, cytoxan, etoposide, ifosfamide, and megace, all of which have been approved for one or more indications in cancer therapy. FDA has authority to control advertising and promotion of substances it regulates, limiting those efforts to approved uses.

That control runs up against the fact that physicians are not limited to approved indications in prescribing drugs, and prescribing anticancer drugs for treatment of other than approved uses is widespread. Also, most cancer chemotherapy involves uses of drugs in various combinations, very few of which have been specifically approved by FDA.

FDA, therefore, is in the tenuous and almost unjustifiable position of attempting to outlaw discussion of legal activities. The agency has ordered Bristol to submit all promotional materials generated by the company's Oncology Division during the next two years to FDA for preclearance before they are distributed. Bristol also was directed to send letters to all physicians who received copies of the publication, "Oncology Commentary 90," sponsored by the company which reported on scientific discussions of off label uses of various Bristol drugs. The letter called attention to FDA's determination that the publication constitutes inappropriate promotion of Bristol products for unlabeled uses; that it and some of the scientific meetings it cited had been sponsored by Bristol; that it included only favorable opinions and comments on the company's products; and that FDA considered most of the opinions and research discussed in the publication were not detailed enough to permit informed evaluation.

"FDA wishes us to emphasize that FDA has not characterized the data referred to in 'Oncology Commentary 90' as adequate or inadequate," the letter said. "FDA has objected to our dissemination of a promotional publication in the guise of a scientific journal."

Bruce Chabner, director of NCI's Div. of Cancer Treatment and a frequent critic of FDA over other issues, called the agency's action "anti-intellectual, unrealistic, and inhibitory to technology transfer."

In a statement to the DCT Board of Scientific Counselors at their meeting this month, Chabner said, "I must state my personal concern about the recent zealous FDA efforts to curb the distribution of meeting newsletters under company sponsorship. Several drug companies have sponsored periodic newsletters describing presentation of research results at important meetings, including the annual cancer meetings of ASCO and AACR. FDA has objected to these newsletters as thinly veiled advertisements for off label uses of approved products, and has forced Bristol-Myers Squibb, as its first target, to mail a letter to physicians admitting its guilt in advertising products for off label use.

"Bristol will be required to suspend all such meeting reports and to obtain FDA clearance for all mailings to physicians for the next two years," Chabner continued. "Now, while it is true that some meetings described in such mailings were concerned solely with drug company products, others represented the best of current cancer research. In the latter instance, the meeting reports were accurate and useful summaries of state of the art research.

"There are a number of contradictions and inconsistencies in the FDA policy. The fact is that therapeutic research, by its very nature, encourages off label use of approved drugs. An article in the 'New England Journal of Medicine' may present evidence that would encourage off label use of a drug, and this is allowed. NCI or a private institution could publicly endorse and disseminate the same information without FDA restriction.

"What really matters is the content of the report, not its sponsorship. The whole episode really calls into question the current FDA policy of approval of drugs for new indications. If FDA is going to be hard nosed about company dissemination of research results, then it needs to devise a more rapid way for approving drugs for [additional indications]. Under current procedures, it is simply not possible for FDA to keep pace with the changing patterns of approved drugs. The package inserts for most drugs bear little relationship to the current use of these agents.

"It is anti-intellectual, unrealistic, and inhibitory to technology transfer to restrict the dissemination of valid research results concerning a new use for an approved drug. I urge FDA to refocus its efforts and specifically to devise an expedited system for approving new uses of approved agents," Chabner concluded.

FDA Commissioner David Kessler, who took office last December, has been credited with the crackdown on supposed improper advertising and promotion. Earlier this year, FDA took action against food labels which it said improperly contend that products were fresh, cholesterol free, fat free, low calorie, etc.

Just this month, Kessler testified at a congressional hearing on off label use of retin-A cream, collagen, and silicone for unapproved cosmetic uses. He warned that action against those practices could include seizure and injunctions, along with prosecution of physicians who prescribe for those uses and company officials who promote them.

The move against Bristol preceded Kessler's appointment, beginning in 1988 with an objection to a promotional piece for etoposide which suggested that it in combination with cytoxan and CeeNU had been effective in treatment of small cell lung cancer in at least once study. Arthur Yellin, assistant to the director of FDA's Div. of Drug Advertising & Labeling, wrote, "Specifically, the piece references combination of your firm's CeeNU and cytoxan products, neither of which are indicated for the treatment of small cell lung cancer. As you know, such a violation not only misbrands [etoposide] but also misbrands both [CCNU] and cytoxan."

Bristol contended that the study discussed in the piece had been pivotal in gaining approval of etoposide and that therefore mention of the combination should be considered acceptable.

FDA continued to press the company over that issue into 1989, and then dropped it when Bristol said that it had no further plans to distribute the promotional piece.

FDA soon came up with another issue, however. Bristol had taped a session on the efficacy of carboplatin vs. cisplatin in suboptimal ovarian cancer at the 1989 ASCO meeting in San Francisco. Discussion was based on a study which suggested carboplatin could be considered for first line therapy of ovarian cancer. Copies of the tape were distributed to physicians by the company.

Since FDA approval of carboplatin was limited to treatment of refractory ovarian cancer, the agency objected. Bristol responded that the tape was unedited, from a plenary session, and that the company had no control over its contents. "Under the circumstances, we believe that dissemination of the unedited presentation in its entirety to those physicians who treat ovarian cancer but who were not in attendance at the ASCO meeting was educational and does not represent promotion of an unapproved use," Richard Hamby, Bristol scientist for regulatory affairs, responded to FDA.

FDA rejected that position and demanded that the company cease distribution of any material suggesting that carboplatin could be used for first line treatment.

The company continued to argue the point, and eventually produced the issues of "Oncology Commentary 90" that brought on FDA's decree.

Although other drugs produced by Bristol have been involved in the dispute, and although FDA has made similar objections to other pharmaceutical companies over supposed inappropriate promotion of their agents, the issue with Bristol most likely was brought to a head over carboplatin. Bristol-Myers Oncology Div. developed carboplatin as a less toxic analog of cisplatin. The company's patent on cisplatin has expired and the desire to come up with a commercially viable successor is obvious.

Carboplatin has little of the nephrotoxicity seen with cisplatin and usually can be administered on an outpatient basis, not always the case with cisplatin. Other side effects seen with cisplatin are absent or diminished with carboplatin.

Clinical studies submitted to FDA in the NDA for carboplatin established those facts, established that responses were equal to (in some cases better) than those of cisplatin, and that disease free survival was equal. However, those studies did not clearly demonstrate an overall survival advantage, and FDA's Oncologic Drugs Advisory Committee declined to recommend approval of carboplatin for first line therapy. FDA went along with ODAC's recommendation, and limited approval to refractory ovarian cancer.

With sufficient scientific basis, physicians have been prescribing carboplatin for first line treatment. Bristol understandably would like that message to get wide distribution.

"All of these off label uses are in the 'Oncology Compendium' and many of them are in PDQ," one Bristol executive said. "In effect, we have the government telling physicians that it is okay to use the drugs for those indications, and then you have another agency of the government telling us that we can't say the same thing."

FDA's rigid enforcement of its advertising/promotion regulatory authority, without considering the nature of the disease, reminds some of the problems the agency had with NCI and clinical investigators in the 1970s and early 1980s over a similar issue. Some FDA regulations are appropriate and well conceived when used to protect against abuses in development and marketing of drugs used to treat nonlife threatening conditions. Those same regulations don't make sense when they block use of a drug in clinical protocols for treatment of patients for whom no other therapy is available and will die without it.

NCI went to the mat repeatedly with FDA over that issue when a series of investigational new drug applications were rejected or held up for relatively innocuous reasons. The two agencies also wrangled for several years over NCI's practice of giving experimental drugs to physicians for compassionate use, a battle that eventually led to the Group C mechanism which permits distribution of unapproved drugs for use in patients not on clinical protocols.

After more than a decade of debate, NCI finally convinced FDA that endpoints other than survival should be considered in approval of a new drug.

The disagreement over the degree to which a drug sponsor may discuss off label uses could be just as crucial. FDA's actions could influence decisions by third party payers on reimbursement for off label uses, a touchy situation even now.

FDA could argue that publications in the scientific literature, presentations at scientific meetings, and listing in PDQ are sufficient to inform practicing oncologists about the potential for unapproved uses. But the fact remains that pharmaceutical companies, with their networks of detail persons in constant contact with physicians, and with their substantial advertising and promotion budgets, may be the primary and in some cases the only information source for many physicians.

DCT Advisors Ok 4 Recompetitions In Developmental Therapeutics

Advisors to NCI's Div. of Cancer Treatment have given concept approval to the recompetition of four major contract programs in the Developmental Therapeutics Program. Altogether, the contracts will cost more than $26 million over five years.

The board also gave its approval to allow a unsolicited application for a "Pediatric Cancer Survivor Study" cooperative agreement to be reviewed by a study section. The application was sent to NCI as a large R01, but the NCI Executive Committee asked the principal investigator to submit it as a cooperative agreement, or U01. The investigator, whose name NCI staff could not reveal, proposes a retrospective cohort study at 29 institutions of about 25,000 pediatric cancer survivors diagnosed between 1970 and 1986 to examine late effects and potential adverse events.

The proposed first year award would be $1.5 million; the trial would last five years. Each institution would receive about $50,000, and the study would count as 29 grants toward NCI's grant target. The board's approval at this stage means the proposed study will go to a study section for review.

Following are the concept statements for the recompetitions:

Iso-Antigenic Typing of Mouse Strains. Recompetition of a contract held by Northwestern Univ. Estimated annual amount $165,000 (75% cancer, 25% AIDS), five years, for a total of $825,000.

The DTP Animal Program supplies inbred, first generation hybrid and immune-compromised rodents to a large number of investigators in the U.S. and around the world. These investigators include NIH intramural users, NCI grantees, and other NCI divisions. A significant portion of the total production effort is directed toward immune-compromised mice for DTP therapeutic studies with human tumors. An animal program of this magnitude must include a quality-control component to identify potential histocompatibility and other problems in the production of inbred mouse strains. The most sensitive method for assurance of histocompatibility with inbred strains involves the use of skin grafting. This assurance is of critical importance to investigators who rely on the DTP Animal Program. This contract performs skin grafts that provide assurance that inbred strains remain histocompatible with NIH-maintained foundation colonies. Major histocompatibility problems are identified within 30 days by this system, but grafts are held for 100 days in order to identify minor problems. The major advantage with this approach to histocompatibility testing is that subtle problems such as mutations (genetic drift) can be identified only through skin grafting.

Yearly, this contract received approximately three percent of the breeders from each foundation, pedigreed expansion, and production colony within our total program. At the same time, depending on availability, animals of the same strain were sent to the contractor from the NIH Repository and used as reference animals. The animals from production contractors were tail-grafted onto NIH reference animals and vice versa. In addition, within-line grafts were done on each source of animals supplied. All of these animals were shipped according to a schedule drawn by the Project Officer.

During the past 3 years this contract identified a few strains of mice with minor compatibility problems, probably due to genetic drift. None of the so-called weak rejectors occurred in the early stages. None of the problems caused any interruption in production. Since all animals from the foundation colonies and the pedigreed expansion colonies were identified by parent, we were able to go to the pedigree charts and eliminate any suspect family and/or line. This identification, by this contract, enabled us to make adjustments before a problem became significant.

Since several strains of mice within the DTP Animal Program are produced at more than one location. This contract confirms that from a genetic standpoint all mice of the same strain are genetically pure regardless of the contract location from which they were sent.

It is our intent to continue this effort for another 5 years. This is necessary to confirm or deny the genetic purity of the mouse strains produced by the Biological Testing Branch (BTB) Program. The new award will be effective December 1, 1992.

Master Agreements for Chemical Synthesis. Recompetition of contracts held by Univ. of Alabama, Pars Pharmaceutical Labs Inc., Research Triangle Institute, Ricerca Inc., Dept. of Scientific & Industrial Research, Southern Research Institute, SRI International, and Starks Associates. Estimated annual amount $450,000 (50% cancer, 50% AIDS), five years, for total of $2.25 million.

The objective of this project is the resynthesis of small amounts of compounds to support our in vitro and in vivo cancer and AIDS screening programs. Compounds that have been identified by our in vitro screens as requiring confirmatory testing or as candidates for secondary testing are resynthesized by well established reported methods. Unique compounds with reported biological activity that are not obtainable from the original source are also candidates for Master Agreement synthesis. Compounds selected for resynthesis cannot be obtained by other means in a timely fashion.

Master Agreements are multiple instruments that are competitively awarded to organizations that are judged to be qualified to compete for future Master Agreement Orders. This pool of qualified organizations may consist of academic institutions, small businesses, research institutions and industries. Master Agreements are designed to accomplish a specific task as promptly as possible.

Master Agreement Holders have the skill and facility to perform a variety of chemical reactions including nucleophilic and electrophilic substitutions, hydrogenations, molecular rearrangements, cycloadditions and photochemical rearrangements. Although innovativeness and proficiency are required to perform these reactions, extensive methodology and basic research are not required.

The complexity of synthesis tasks varies widely from simple synthetic compounds to complex natural products. The quantity of compounds for synthesis ranges from 20 mg to 2 gm. Compounds are characterized as to their identity by IR, UV, NMR and elemental analysis and conform to required levels of purity and homogeneity.

An average of 200 compounds per year have been synthesized under the Master Agreement for Chemical Synthesis mechanism. These compounds have been structurally diverse. Compounds synthesized under this project include those for confirmatory testing and secondary testing in the various screens, requests from intramural staff, and compounds from the literature with known biological activity. This project for the resynthesis of compounds to the program has proved to be extremely cost effective.

Through the Master Agreements, we are proposing to resynthesize approximately 120 compounds per year to support our new anticancer and anti-AIDS drug discovery programs on an as-needed basis in a flexible, cost-effective manner. Presently, we are acquiring small amounts of compounds sufficient for the primary in vitro screen only. The leads identified by the primary screen must be synthesized in larger amounts for secondary testing. Now that both in vitro screens, cancer and AIDS, are testing compounds at the rate of 10,000 each per year, it is essential to have this flexible, cost-effective program to support the screening effort.

Preclinical Toxicology and Pharmacology of Drugs Developed for Cancer, AIDS, and AIDS-Related Illnesses. Recompetition of contracts held by Midwest Research Institute, Southern Research Institute, and Springborn Laboratories Inc. for anticancer preclinical toxicology, and Battelle Columbus Laboratories and Southern Research Institute for anti-AIDS preclinical toxicology. Estimated annual amount $4.22 million (50% cancer, 50% AIDS), five years, total $21.1 million.

Toxicology studies include the following major objectives:

-Determination and safety assessment of a clinical starting dose.

-Determination of dose limiting toxicities (DLT).

-Determination of a maximum tolerated dose (MTD).

-Determination of the reversibility of adverse effects.

-Determination of schedule-dependent toxicity.

In addition to these objectives for both anticancer and anti-AIDS drugs, studies designed to evaluate the toxicity of anti-AIDS

drugs also include the following:

-Determination of whether the antiviral EC

$_{50}$ can be attained in plasma in vivo.

-Determination of whether the drug crosses the blood-brain barrier.

During the course of the ongoing contracts, the emphasis of preclinical toxicology studies has continued to shift away from the use of standardized protocols (such as Dx1 and Dx5 studies by intravenous administration) to evaluate the potential adverse effects of new anticancer and anti-AIDS agents. Current practice involves designing and performing agent-directed studies within a pharmacologically-guided framework. This is accomplished through the acquisition and use of pharmacokinetics information to reliably extrapolate toxic effects across species by relating plasma drug levels [peak and steady state and/or area-under-the-curve (AUC)] to safety and the occurrence and severity of toxicity. Integration of these studies with efficacy data and the proposed clinical protocol permits a more rational evaluation of the role of schedule dependence and pharmacokinetics in the development of toxicity.

In addition to this philosophical change in the approach to the development of toxicity information, the development of drugs within DTP has evolved into two stages that each require a toxicological evaluation. The first involves a preliminary assessment of toxicity in mice and dogs with the determination of MTD in both species and pharmacokinetics in dogs. (Pharmacokinetics in rodents is determined separately by the Pharmacology Branch of the DTP.) If the drug meets the program criteria for full-scale development, a more complete toxicity evaluation is performed as described above that will lead to the filing of an IND. This two-step approach allows the program to determine if full development is reasonable with a limited expenditure of resources (drugs, animals, and dollars).

The new approach to toxicity evaluation has necessitated the development of new techniques such as the following: 120-hour continuous intravenous infusions in rats, 30-day continuous intravenous infusions in dogs, and q8h x 15 intravenous injection studies in mice. Routes of administration used in these studies include intravenous, oral, subcutaneous, intramuscular, and intraperitoneal. New vehicles evaluated include 20 percent Liposyn II, 70 percent DMSO, PEG 300 and 400, propylene glycol, sesame oil, and a specially formulated fat emulsion as well as other routine and not so routine vehicles for IV administration. Data on plasma concentrations, volume of distribution, apparent steady state plasma concentrations, and total body, renal, and nonrenal clearance values were determined for each drug to assist in pharmacologically-guided dose escalation in the clinic.

There is a continuing requirement to carry out toxicology and pharmacology studies on the new agents, both anticancer and anti-AIDS, prior to the initiation of clinical studies. For recompetition, the contract requirements will be advertised essentially as presently documented except as noted below. In the past, these contracts evolved from separate concepts for cancer and AIDS that were previously presented to the Board of Scientific Counselors for approval. They are being combined at this time to afford the Toxicology Branch the greatest flexibility in assigning studies to the most appropriate contractor and to realize a cost savings to the program in the form of reduced contract administrative costs. Each of the four anticipated awards will be able to evaluate two to three drug candidates per year.

The Toxicology Branch is also separately exploring the use of murine versus human bone marrow stem cells as an in vitro assay system to evaluate the hematological toxicity of both anticancer and anti-AIDS drugs. Results from these studies are compared to the bone marrow toxicity observed in vivo. Additional in vivo/in vitro studies are necessary to bridge the gap between pure in vivo and pure in vitro studies and provide the basis for fully evaluating the in vitro assays and correlating the data obtained with that determined in human clinical trials. It is the intent of the Toxicology Branch to perform this evaluation under these contracts as part of the full toxicological workup of each drug that has been shown to be myelosuppressive in preliminary studies. This type of data will also form the basis for the evaluation of other in vitro assays as a way to reduce the resources necessary to evaluate a drug from a toxicological point of view prior to instituting human clinical trials.

Due to the fact that so many anticancer drugs and some anti-AIDS drugs are myelosuppressive, the Toxicology Branch in collaboration with the Investigational Drug Branch of CTEP is considering the use of cytokines as a way to ameliorate myelosuppression as the dose limiting toxicity in preclinical toxicity studies. Additional dose escalation might then be possible and could result in the detection of other dose limiting toxicities that would otherwise be missed. This could be of great benefit in the clinical evaluation of the drug.

Maintenance of the NCI Drug Information System. Recompetition of a contract held by Fein-Marquart Associates. Estimated annual amount $442,000 (50% cancer, 50% AIDS), five years, total $2.21 million.

The NCI Drug Information System (DIS) provides computer support for operations of the Developmental Therapeutics Program. DIS manages every step a test compound takes from acquisition to shipment to the biological screens. After screening, DIS is consulted to determine what chemical structure was screened, what similar structures were previously screened, what similar structures are in the database, and which of them have inventory remaining. It is the system from which all chemical structure and substructure searching of synthetic compounds and purified natural products takes place. It is where all information concerning the source and identity of all natural product samples and extracts are stored and queried. All sample supplier information is entered, stored, and used from DIS. All sample inventory records are entered, stored, and incremented from DIS. All sample shipping is requested through DIS and tracked by it. Much of the correspondence sent to suppliers about their compounds is generated by DIS. DIS also records to whom and to where supplier reports are sent once screening of a sample is completed. Essentially everything NCI knows about the 30 years worth of synthetic compounds (currently there are 563,750 samples of 441,000 NSC numbers) or natural product extracts (285,600 extract/samples obtained to date from 31,250 raw materials) that NCI has acquired and tested, were entered into, reside in, and are accessible from DIS. In addition, much of the in vivo test data amassed over the last 30 years are obtainable from DIS. The in vitro anticancer and anti-AIDS test data are not in DIS but are contained in other NCI databases.

The system consists of three major components. The first is the Chemistry System. This system provides computer support for the chemistry database and the chemical structure and substructure search systems. Special subsystems and modules of the Chemistry System support the acquisition and storage of synthetic and refined natural product compounds. The second is the Pharmaceutical Data System (PDS). PDS provides computer support for the acquisition and development of clinical drugs. The third is the Natural Products Repository Support System (NPRSS), which provides computer support for the acquisition, preparation, and storage of crude natural product extracts.

The objective of this contract effort is to maintain and develop DIS to meet the changing demands of the Developmental

Therapeutics Program. The maintenance will include enhancing the software to perform additional functions, correction of errors, and the performance of operational tasks required for database correctness.

The development of DIS was begun in 1982 as part of a joint effort with the Environmental Protection Agency. The system was originally designed and developed by Fein-Marquart Associates, which subsequently won the competition award for the maintenance of DIS. Maintenance of DIS has been carried out since mid-1985 under this and a predecessor contract. During this time, DIS has been available to users for over 99 percent of the computer's service time, which is normally 24 hours per day, 7 days per week. The system was initially installed on a DEC system 10, a now obsolete computer that was operated by the DiV. of Computer Research and Technology in Bethesda. In 1989, the software was converted to the DTP VAX computer system in Frederick, MD.

This effort will have the primary responsibility for providing operations and programming support necessary for the continued availability and accuracy of DIS. The tasks will include development of software enhancements, corrections of erroneous algorithms, and database maintenance.

The current state of the art in computer-assisted drug discovery and development utilizes three-dimensional representations of chemical structures. DIS uses two-dimensional chemical structures. DTP is currently evaluating the Concord product to assist in the conversion of the database to a 3-D form.

A major activity will be the modernization of DIS. The thrust of this effort will be to use a commercially available relational database package.

Currently, the database software for DIS is an FMA-developed product called XTDRS. The software consists of a large complex library of FORTRAN programs. Over the years, this system of program has evolved into a highly functional, high performance, specialized tool designed to meet DTP's unique computer system requirements. It does its job very well at this time with some important reservations.

A major disadvantage is a difficulty integrating the in vitro screening data system (or any non-DIS system) with the chemistry data system. Another disadvantage is that DTP bears the entire cost of technical upgrades to the product.

DTP decided in 1988 to develop its in vitro cancer and AIDS database systems using a commercial relational database product known as ORACLE, and DTP has since used the ORACLE system for several other important projects. In 1990, under a separate contract, the NPRSS was rewritten as an ORACLE based system replacing the XTDRS system written in FORTRAN. The success of this relatively small conversion will encourage and assist a much more ambitious project to combine an ORACLE database system with a chemistry structure and substructure search system for the modernization of the Chemistry System and PDS. This conversion, now only in the preliminary planning stage, will require several years to complete.

NCI Advisory Group, Other Cancer Meetings For July, August, Future

Longterm Antihormonal Therapy for Breast Cancer--June 30-July 2, Lake Buena Vista, FL. Contact International Conference Headquarters, PO Box 30,000, Philadelphia, PA 19103, phone 800/735-8450 or 215/735-8450.

FDA Oncologic Drugs Advisory Committee--July 1-2, Rockville, MD, Parklawn Bldg., 5600 Fishers Ln., Conference Rms D and E, open 9 a.m. July 1 and 8:30 a.m. July 2. Drugs on agenda: tenoposide, carboplatin, leucovorin, pentostatin; also discussion of NSABP tamoxifen breast cancer prevention protocol.

Tumor Hypoxia Workshop--July 2-5, Orillia, Ontario, Canada. Contact Dr. Ian Tannock, Ontario Cancer Institute, phone 416/924-0671.

International Congress of Radiation Research--July 7-12, 1991, Toronto, Canada. Deadlines: Junior Investigators Awards, Oct. 15; Abstracts, Jan. 15, 1991. Contact International Congress of Radiation Research, 1891 Preston White Dr., Reston, VA 22091, phone 703/648-3780.

President's Cancer Panel--July 9, NIH Bldg. 1, Wilson Hall. Open 8:30 a.m.-noon. Topic is "Cancer and Poverty."

British Assn. of Surgical Oncology--July 12-13, Sheffield, UK. Contact BASO, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN, UK.

Breast Disease: Diagnostic Imaging & Current Management--July 14-17, Grand Traverse Village, MI. Contact Angela Voeller, Office of Continuing Medical Education, G-1100 Towsley Center Box 0201, Univ. of Michigan Medical School, Ann Arbor, MI 48109, phone 313/743-2288.

Clinical Problems & Solutions in Ovarian Cancer--July 18, Indianapolis, IN. Westin Hotel. Contact Carol Lewis, Indiana Univ., Div. of Continuing Medical Education, 1226 West Michigan BR 156, Indianapolis, IN 46202, phone 317/274-8353.

International Society for Experimental Hematology--July 21-25, Parma, Italy. Contact Dr. Vitorio Rizzoli, Universita di Parma, Via Gramsci, 14, 1-43100 Parma, Italy, phone 0039-521-290787, fax 0039-521-292765.

Soft Tissue Sarcoma Review Course--July 24-27, Keystone, CO. Contact Jeff Rasco, Conference Services, Box 131, 1515 Holcombe Blvd., Houston, TX, phone 713/792-2222.

American Assn. for Clinical Chemistry Annual Meeting--July 28-Aug. 1, Washington, DC. Contact Nick Ryerson, 800/892-1400 or 202/835-8718.

Enterostomal Therapy Nursing: Across the Life Span--Aug. 12-13, Cleveland, OH. Contact Cleveland Clinic Foundation, Dept. of Continuing Education, PO Box 94977, Cleveland, OH 44195, phone 216/444-5696 or 800/762-8173.

Oncology Nursing Certification Exam Review--Aug. 16-17, Tampa, FL. Contact St. Joseph's Cancer Institute, 813/870-4320.

Beijing Blood Cell Growth Factors Symposium--Aug. 21-24, Beijing, China, Beijing International Hotel. Contact Dr. Ann Murphy, Hipple Cancer Research Center, 4100 South Kettering Blvd., Dayton, OH 45439-2092, phone 513/293-8508 or fax 513/293-7652.

Future Meetings

Immunobiology of Renal Cell Carcinoma--Oct. 21-11, Cleveland, OH. Contact the Cleveland Clinic Education Foundation, PO Box 94977, Cleveland, OH 44195, phone 800/762-8173 or 216/444-5696.

Family Medicine for the '90s--Oct. 23-26, Houston, TX. Contact Amy Zandy, Texas Academy of Family Physicians, 8733 Shoal Creek Blvd., Austin, TX 78758, phone 512/451-8237.

Leukemia Society of America Medical Symposium--Nov. 1-2, St. Louis, MO. Contact the society, phone 212/573-8484.

Concepts and Molecular Mechanisms of Multistage Carcinogens--Nov. 6-9, Santa Margherita, Italy. Contact American Assn. for Cancer Research, Public Ledger Bldg. Suite 816, Sixth & Chestnut Sts., Philadelphia, PA 19106, phone 215/440-9300.

Prostate Cancer: Screening and Treatment Controversies--Nov. 15, Chapel Hill, NC. Contact Office of CME, CB #7000, 231 MacNider Bldg., UNC School of Medicine, Chapel Hill, NC 27599, phone 919/962-2118 or 919/962-1664.

Advances in Biology and Clinical Management of Melanoma--Nov. 19-22, Houston, TX. Contact M.D. Anderson Cancer Center, 713/792-3030.