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Fred Hutchinson Center Wins $140 Mil. Contract To Coordinate NIH Women's Health Initiative

Fred Hutchinson Cancer Research Center in Seattle has won a $140 million, 15-year contract to launch the NIH Women's Health Initiative. The center will serve as the clinical coordinating center for the initiative.

Ross Prentice, director of the center's Public Health Sciences division, is the principal investigator, and Maureen Henderson, head of the

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In Brief

The Anatomy Of An Administrative Nightmare: How NIH Spent $518 Million In One Day

LEO BUSCHER, chief of NCI's Grants Administration Branch, was faced with a management problem unlike any other when Congress last year included $518 million in the NIH FY 1992 appropriations that could be spent on only one day, the last day of the fiscal year. The "delayed availability" allowed Congress to avoid exceeding spending limits. Buscher, branch chief since 1972, is credited with developing the system that got the money out smoothly; he devised the process for doling out NCI's portion of the delayed funds, $196 million, but his method also was used by 16 of the 18 institutes. "It was a group effort," he told **The Cancer Letter**. How it worked: Buscher and NCI colleagues, with the NIH Div. of Research Grants, developed a parallel system within the regular obligating system so that the awards process was completed and sent to the DRG computer system, and coded for a special tape that was put on hold. "We were able to build on the tape throughout the summer, and add awards onto it daily, and make adjustments when we had to," Buscher said. On the 30th, the tape was run and 310 grant awards were mailed. **Sounds easy?** NCI had to issue split awards for some grants with start dates earlier than September; some grantees got "short" awards prior to Sept. 30; at the same time, NCI prepared another award notice. "No one complained, as far as I know," Buscher said. "They were somewhat at risk if that tape had blown." **Buscher's fear** was real: minutes of an NCI Executive Committee meeting stated, "There can be no mistakes on this system." Said Buscher: "I was having nightmares." A pilot test in early spring showed that the system could work. In the end, it was business as usual. NCI's Div. of Financial Management ran the tape at the end of the day on the 30th, as if it were businesss that occurred that day. "They are bold over there," Buscher said. NIH FY93 budget does not include delayed funds. Just as well, Buscher said. "It would be nice if [delayed availability] does go away."

Fred Hutchinson Center Wins $140M Contract To Coordinate WHI Trials

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center's Cancer Prevention Research program, is co-principal investigator.

The center ultimately will oversee a network of 45 clinical centers nationwide carrying out the initiative, which will be made up of clinical and observational studies to evaluate treatment and prevention strategies for coronary heart disease, cancer, and osteoporosis in more than 150,000 postmenopausal women. The full initiative will cost $625 million.

The initiative was proposed in 1991 by NIH Director Bernadine Healy soon after she was sworn in, but Prentice and Henderson spent years trying to convince NCI to study dietary factors in prevention of breast cancer, finally culminating in the Women's Health Trial Feasibility Study. Hutchinson was awarded the $4.4 million contract to conduct the Women's Health Trial Feasibility Study in Minority Populations, to assess methods and success rates for recruiting minority women to the nutrition education and behavior modification study. The results of the feasibility study will be used to improve WHI recruitment and dietary intervention methods.

"The NIH Women's Health Initiative is a project of national importance that is both unprecedented and overdue," HHS Secretary Louis Sullivan said in a statement. "Health research for women is finally moving toward the equal status it deserves."

The coordinating center, Healy said, "will function as the central nervous system" of the initiative. "The Hutchinson Center has extensive experience in coordinating large medical research trials, especially dietary interventions," she said. "It has distinguished itself in the management of other NIH clinical trials of women."

The first 15 of the 45 clinical centers will be selected early in 1993, while the remaining 30 are expected to be announced early in 1994. The first 15 centers will develop, implement and refine the overall program for the initiative.

The objectives of the clinical trials are to test the benefit and risk of hormone replacement therapy, dietary modification, and supplementation with calcium plus vitamin D on the overall health of postmenopausal women age 50-79. With some overlap of participants in the different studies, approximately 57,000 women will participate in the clinical trials.

The goals of the observational study will be to improve risk prediction of coronary heart disease, breast cancer, fractures and total mortality in postmenopausal women, to examine the impact of changes in characteristics of disease and total mortality, and to create a resource of data and biological samples which can be used to identify new risk factors and/or biomarkers for disease. About 100,000 women will be participants in the observational study.

Recruitment for the studies will begin after about 10 months of planning and training.

The coordinating center will be made up of three units: clinical nutrition and intervention, statistical and central study, and leadership. The Hutchinson Center will also handle a number of subcontracts for scientific groups handling blood imaging and other special measurements.

Major subcontractors are the Univ. of Washington, Bowman Gray School of Medicine, the Univ. of San Francisco, the Univ. of Minnesota, the Univ. of Alberta, and Ogden Bioservices.

NIH has $21.6 million this year to begin the initiative.

The statistical and central study unit proposed an advanced computing system that will link all clinical center sites directly to the clinical coordinating center via a wide-area network on dedicated high-speed lines.

"To our knowledge, no other multicenter clinical trial has ever proposed such a system," WHI biostatistician Garnet Anderson said to "Nucleus," the center's newsletter.

"Assuring the integrity of a study involving so many organizations and individuals requires a strong, proactive management and coordination effort," Anderson said.

The project will create 25 to 30 new positions at Hutchinson, equivalent to 10 full-time positions. Plans are underway to renovate one floor of the center to house the coordinating center's offices.

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Editor: **Kirsten Boyd Goldberg**
Founder & Contributing Editor: **Jerry D. Boyd**
Associate Editor: **Paul Goldberg**

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

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Illinois, California Enact ACCC Model Law On Reimbursement

Illinois and California became the third and fourth states to enact health insurance reimbursement regulations based on the model bill developed by the Assn. of Community Cancer Centers.

The new state laws require that insurers operating in those states rely on the three drug compendia rather than the indications on the package insert as a guide for reimbursement for cancer care.

Similar legislation was passed in New York and Michigan last year. Another such bill is under consideration in Massachusetts.

"The issue allows all cancer groups to come together and confront a common problem: quality cancer care and our ability to provide it," Jamie Young, ACCC director of public policy, said to **The Cancer Letter.**

Lobbying for the bills, ACCC has been working with the state chapters of the American Cancer Society, state oncology societies, hospital associations, the Oncology Nursing Society and the National Coalition for Cancer Survivorship, Young said.

The California measure is unique because it mandates off-label reimbursement in the treatment of cancer as well as other life-threatening diseases, particularly AIDS.

Though opposed by the state's insurance industry, the California bill was approved by a 6-1 margin last summer and signed by Gov. Pete Wilson.

In Illinois, the bill's proponents negotiated an agreement that removed the state insurance industry's opposition and the bill cleared the House and Senate without a single nay vote. According to Young, **ACCC president Robert Clarke** was instrumental in winning the support of the Illinois Hospital Assn., which gave the bill a strong endorsement.

An overview of similar measures in other state legislatures follows:

--An off label reimbursement bill is expected to be introduced next fall in **Arizona**'s legislature. ACCC is working with the Arizona Clinical Oncology Society and ACS to introduce the legislation.

--**Colorado**'s Rocky Mountain Oncology Society is collecting input from its members to assess the extent of off label denials and to gauge the physicians' interest in approaching the legislature.

--In **Georgia**, the state's ACS chapter and ACCC hope to have a bill introduced next year, Young said.

--Responding to physician concerns about reimbursement policies of the **Hawaii** Medical Service Assn., the Blue Cross/Blue Shield carrier, several groups got behind a bill patterned on the ACCC model legislation. With the measure pending, HMSA signed an agreement to reimburse off-label use, Young said. Since the agreement was reached, cancer patients began receiving access to treatments that were being denied a year earlier, he said.

--In **Indiana**, the legislature adjourned Feb. 14, concluding the shortest session in history and leaving an off-label bill among its unfinished business. Preparing for reintroduction next year, ACCC recently organized a meeting of the bill's strongest supporters.

--An off-label reimbursement bill sponsored by a cancer survivor, Sen. Nancy Sullivan, was pending in **Massachusetts.** According to Young, Sullivan was "planning to expose, in a very public way, insurance companies and legislators alike for being against cancer patients."

--An off-label reimbursement bill was defeated in **Minnesota**'s legislature, but the bill's sponsor, Rep. Alice Hausman, vowed to try again next year.

The three compendia are published by U.S. Pharmacopeial Convention, American Medical Assn. and the American Society of Hospital Pharmacists.

Wyden, Schroeder Bill Requires NIH To Test RU 486 For Breast Cancer

House members Ron Wyden (D-OR) and Pat Schroeder (D-CO) introduced a bill that would require NIH to test RU 486 as an abortifacient as well as in other indications including breast cancer.

In an announcement that accompanied the bill, HR 6178, Wyden and Schroeder said NCI's response to an earlier congressional request for information contained an admission of policy to suppress the trials of the agent for breast cancer.

NCI officials said no such policy ever existed and the agent did not undergo trials because it failed to spark sufficient interest on the part of investigators.

"It is cruel and counterproductive to suggest that a physician at NCI would allow a political ideology to prevent the development of [RU 486]," Bruce Chabner, director of the NCI Div. of Cancer Treatment, said to the division's Board of Scientific Counselors this week.

"I can assure you that I would be the first to leave my position if that were the price of working at NCI," said Chabner, who bore the brunt of the attack.

The DCT board planned to write a letter protesting what several members described as a dangerous attempt by politicians to set scientific priorities.

This latest round of controversy began with Wyden's Aug. 10 letter to Chabner, in which the congressman demanded that NCI explain its "failure to

pursue much needed research on an important new drug for a disease that claims tens of thousands of American lives each year."

Wyden's request for information referred to a letter by the president of the Roussel-Uclaf, the drug's sponsor, who stated that "The American NCI, having other promising compounds to be tested, did not want to be immediately involved in this study" (**The Cancer Letter**, Sept. 4).

In a letter dated Oct. 2, Chabner provided the anatomy of the decision not to pursue the study of RU 486, but left open the possibility that the Institute would conduct a trial if new data becomes available and if investigators show interest.

Introducing their bill six days later, Wyden and Schroeder said they obtained documents showing that NCI "denied a major breast cancer research trial using RU 486, even though agency researchers said the drug held promise for fighting breast cancer."

In a press release, the two House members said that NCI's "claim that U.S. researchers are disinterested in the drug's potential for fighting breast cancer is simply false."

Several days later, Chabner and Wyden restated their positions on the CBS morning news program.

This week, Chabner addressed the controversy to at a meeting of the board of scientific counselors.

The text of Chabner's statement follows:

In 1991 we were approached by Roussel-Uclaf, a French drug company, regarding possible interest in testing their anti-progestin, RU 486, against breast cancer.

We reviewed the data they provided, including several papers that described a few short-lived responses in patients who had failed other endocrine therapies. We asked outside investigators for their level of interest, and concluded that rather than embark on new trials, we would wait to see the results of ongoing company trials in Canada and France.

Additional reasons for our moderate enthusiasm for new trials included (1) the existence of approved progestin therapy, megace; (2) the greater priority of other agents, including new drugs such as taxol, rhizoxin, navelbine, camptothecins and anthrapyrazole, all of which have activity in breast cancer.

In late August I received an inquiry from Congressman Wyden asking if political considerations, such as the drug's abortifacient actions, had led us not to study this drug for breast cancer. I replied as above, but added that we, in fact, have initiated a trial in meningiomas, and will be eager to reconsider breast cancer trials if there is interest on the part of NCI grantees.

In a press release on Oct. 8, Congressman Wyden's staff concluded--for reasons that escape me--that our reply provided evidence that political considerations led to the decision not to support the trial.

Let me say unequivocally that this is not true. The Administration has never asked us to forebear from studying this drug for cancer. In fact, as I stated, we are supplying RU 486 for the treatment of a form of brain tumor, and the drug is being used in four other non-cancer protocols in the Clinical Center. The fact that it has abortifacient properties had no bearing on this decision.

Many of the drugs we are studying have abortifacient properties, including methotrexate, which is commonly used for aborting ectopic pregnancies. I might add that this use of methotrexate is based on the work of my laboratory and others demonstrating its avid polyglutamation in placental tissue.

We met with a representative of the company last week and reviewed the slow accrual to ongoing trials of RU 486. The company representative suggested, and we agreed, to reconsider cosponsorship of a trial one year from now, when the Canadian and French are near completion.

Mr. Wyden's press release stated that investigators at Sloan-Kettering, Georgetown and the Medical College of Virginia were thwarted in their attempts to study the drug by NCI.

I have spoken with appropriate officials at each of these institutions. None has ever requested our support. David Goldman, the Director of the Cancer Center at the Medical College of Virginia, has stated that his institution has no current interest in testing RU-486. Larry Norton, the head of the breast cancer service at Memorial Sloan-Kettering, has not proposed a study and has no current interest in one. Marc Lippman, at the Lombardi Cancer Center, did not express interest when asked one year ago, but last week indicated that he would undertake such a trial if the drug were available. We have written to Dr. Lippman to indicate that we will offer our help, if the company is interested.

Rep. Wyden and Rep. Pat Schroeder have introduced a bill that would require NCI to test RU 486.

Obviously, we will comply with the wishes of Congress. We agree that potentially useful drugs should be available for research trials, but the decision to do such trials, whether for cancer, abortion or any other use, should be based on science, not politics.

We are in active discussion with a second company regarding the testing of a new antiprogestin, and will

again survey our grantees to determine their level of interest. Let me assure you that we will support any scientifically valid and worthwhile study, irrespective of the other possible uses of any such drugs.

DCT Board Approves Small Grants Program For AIDS Malignancies

NCI's Div. of Cancer Treatment plans to continue a small grants program that will set aside $1.5 million over the next two years for novel phase 1 and 2 clinical trials in AIDS malignancies.

DCT's Board of Scientific Counselors this week gave concept approval to the proposed RFA, as well as recompetition of three contracts worth nearly $9 million over the next five years. Two other concepts had not received approval by presstime this week; they will be published in next week's issue.

A contract recompetition proposed by Surgery Branch Chief Steven Rosenberg was tabled until the board's next meeting scheduled for February. OTC Biotechnology Research Institute currently holds the contract to provide the branch with tumor-infiltrating lymphocytes for administration to patients in Surgery Branch protocols. The firm will receive $1.18 million this year to provide the services; Rosenberg proposed an increase in the recompetition to $1.3 million per year for three years. The cost of materials for one lymphocyte culture is $8,716.50.

Following are the approved concept statements:

[Reports on concept reviews by the boards of scientific counselors of NCI divisions provide readers with advance notice of the Institute's spending plans. Notices of Requests for Proposals, Requests for Applications, or Program Announcements are published in **The Cancer Letter** as they are released; proposals need not be submitted until that time.]

DCT Small Grants to Stimulate Novel Phase I/II Clinical Trials in AIDS Malignancies. Proposed RFA, first year award $750,000, total $1.5 million over two years, 100% AIDS funding.

Congenital and acquired states of immunodeficiency increase the incidence of high-grade B cell non-Hodgkin's lymphoma, Kaposi's sarcoma, and certain types of epithelial malignancies. Individuals infected with HIV have a marked increase in the appearance of intermediate and high-grade B cell NHL and Kaposi's sarcoma and show trends for an increased incidence of Hodgkin's disease, anogenital dysplasia and cancer, and basal cell carcinoma compared with age-matched controls.

The tumors in HIV-infected individuals are generally aggressive and insufficiently sensitive to conventional therapy. The median survival of HIV-associated NHL is less than 1 year and is only 2 months for primary central nervous system lymphoma. Clinical observations suggest that Hodgkin's disease, anogenital dysplasia and cancer, and basal cell carcinoma have a different natural history and therapeutic outcome compared with the disease in the general population. The dramatic growth rate of the tumors, combined with the problems of myelosuppression and opportunistic infections, has made treatment extremely difficult. As children and adults with HIV infection are surviving longer because of improved retroviral and opportunistic infection treatment, the incidence of the malignancies is expected to rise.

Research into the pathogenesis of these tumors in the context of HIV has shed light on potential interactions of cytolcines, HIV, other viral cofactors (i.e., human papillomavirus in squamous cell cancer of the anogenital region and Epstein-Barr virus in the high-grade primary central nervous system lymphomas), and oncogenes. Based on current information on the potential interactions in the formation of these tumors and the lack of effective, standard regimens, NCI is encouraging investigators to apply novel therapies or innovative approaches in pilot or Phase I and II clinical trials.

The project will fund single or multiple institutions to perform innovative therapeutic studies in AIDS malignancies. The studies should be restricted to pilot or Phase I or II trials, with 5 to 25 patients/trial. Examples of potential clinical studies to consider are (1) combinations of interferon-a and/or retinoic acid in anogenital dysplasia or cancer (recent report by Lippman and associates of a 68 percent response rate in patients with cutaneous squamous cell cancer and a 50 percent major response rate in patients with locally advanced squamous cell cancer of the cervix); (2) antiangiogenesis inhibitors in Kaposi's sarcoma; and (3) immune-modulating therapy with IL-4 (and subsequent down-regulation of IL-6, which may have some role in the development of NHL or Kaposi's sarcoma), anti-B4 blocked ricin immunoconjugate in NHL, or antisense to potential viral cofactors such as human papillomavirus in Kaposi's sarcoma.

The investigators are not limited to the above studies, and any innovative therapies with appropriate rationale are sought.

The major goal of this request for small grant applications (R03) is to develop more effective management and therapies for HIV-associated malignancies in children and in adult men and women. Although the major purpose of these grants is to facilitate rapid testing of novel agents or innovative approaches, the collection of tumor tissue or other relevant biologic fluid will be strongly encouraged for ongoing or future investigations of laboratory correlates. The interchange of ideas and potentially of tumor tissue among the recipients of the grants will be encouraged.

Neuropsychological Testing for Children and Adults with HIV Infection. Recompetition of a contract held by Medical Illness Counseling Center, estimated annual amount $375,000; total $1.125 million over three years, 100% AIDS funding.

During the last 5 years, the Pediatric Branch has established itself as an international leader in Pediatric AIDS research. The Branch has been a world leader in the study of the clinical manifestations associated with HIV infection, the laboratory investigations into the pathogenesis of these manifestations, and the evaluation of new treatments. Dementia, encephalopathy, and neuropsychological deficits are wellrecognized manifestations of infection of the central nervous system (CNS) by HIV in both children and adults. The number of children (particularly vertically infected) and adults with HIV infection is expected to continue to rise. Children as well as adults are at high risk for developing neurological/behavioral abnormalities caused by the effects of HIV infection on the CNS because the virus is neurotropic and the CNS may act as a sanctuary. Therefore longitudinal assessment of neuropsychological functioning is essential to monitor the natural history of this expression of the disease and to determine the optimal point to start therapy and to document benefits of therapeutic interventions.

The Pediatric Branch plans to continue to document through longitudinal studies the natural history of developmental progress

in behavior, cognition, and motor abilities of patients with HIV infection and to investigate the effect of therapeutic interventions on these functions. Because antiretroviral agents have variable absorption rate and different permeabilities into the CNS, pharmacokinetic factors (as well as systemic versus intracerebral effects) will be related to changes in neurobehavioral function.

The Branch plans to continue the search for prognostic factors that may predict change in neurobehavioral function as well as disease progression, with (or without) therapy, and to aid in the determination of the factors underlying the pathogenesis of HIV-associated encephalopathy by providing further characterization of the clinical abnormalities and classification of patients into well defined subgroups. The Branch plans to advance the understanding of brain-behavior relations in this disease by relating physiologic brain abnormalities to behavioral defects. Neurobehavioral measures will be related to neurological (brain imaging), biochemical, virological and physiological variables to study the pathogenesis of the encephalopathy.

The Branch plans to study the specific vulnerability of expressive behavior (expressive versus receptive language, expressed versus perceived emotion, and motor skills) to the effects of HIV infection in children.

Finally, the development and evaluation of interventions (both behavioral and pharmaceutic) to ameliorate the neurocognitive deficits associated with HIV encephalopathy is planned in children and adults.

Operation and Maintenance of the DTP Biological Data Processing System. Recompetition of a contract held by Capitol Technology Information Services Inc. Estimated annual amount $716,000; total $3.58 million over five years (50% AIDS funding, 50% cancer).

In the mid-1980s, NCI changed the nature of its primary screening program. The computer systems then in place to capture, store, analyze, and distribute the data created by the previous in vivo primary screening program were made obsolete by the change. The predecessor contract attempted the first in vitro cancer database design consisting of several flat files, but this design proved inadequate and was discarded when NCI cancer databases were moved from the timeshared IBM system to the dedicated VAX in February 1990. The new database design incorporated a modern commercial relational database management system (ORACLE). The development of the relational database design began in early 1989 as a joint effort involving the AIDS database contractor and individuals selected from other Developmental Therapeutics Program (DTP) contracts. Development of the database systems was continued under the current cancer database contract. The new design was in place by April 1990, and it became operational by June 1990.

There are currently two biological database contracts. One supports AIDS database development, maintenance and operation; and the other supports cancer database development, maintenance, and operation development. We propose to consolidate them into a single contract under the recompetition at a reduced overall level of funding. The AIDS contract began one year earlier than the cancer contract and therefore will end one year earlier, on January 31, 1994. The continuing requirement for AIDS database support will be assumed by the current cancer database contract for 8 months. This additional activity within the cancer database contract will be funded by accelerated spending. This will require a 4-month forward adjustment of the award date for the cancer contract.

The primary responsibility of the contractor is to maintain the various biological database systems. The primary cancer in vitro screening database contains test results for some 12,000 natural product extracts and 25,000 synthetics. The single dose cancer prescreen database contains test results for over 31,000 natural product extracts. The primary AIDS screen database has test results for over 38,000 synthetic compounds and 45,000 natural product extracts.

The two database contracts together have established a successful system of databases and data processing subsystems for the AIDS and cancer in vitro data. In addition to the main cancer and AIDS databases, auxiliary database systems have been developed, including the prostate cell strain project at Stanford; natural product extracts tested initially at a single fixed dose; and a syncytial forming assay secondary test system for the AIDS program.

Special subsystems have been developed to support the drug preparation laboratory activities, support the screening laboratory drug assignment process; maintain information on the fractionation of natural products; track in vitro combination studies; manage information about in vivo supplier reporting; calculate a variety of statistical parameters used for data analysis and for in vitro supplier reports; and record decisions and manage action items for the Biological Evaluation Committee. A pattern-recognition system to help manage repeat testing and selection of actives in the AIDS program was developed.

The most critical task of this effort will be maintenance and operational support of existing systems. Operational responsibility includes editing changes to data, reviewing database update jobs, identifying and resolving problem data, and tracking delinquent data. The contractor will be responsible for adapting existing systems for new in vitro assays. The contractor will adapt the systems to new technologies. There are plans to upgrade the existing system to an upcoming release of the ORACLE system. The new system will provide many new features that will enhance the performance and reliability of the various databases. This project will also provide support for the addition of new functions for enhancement of existing systems.

Several new initiatives are planned for this project: upcoming release of the ORACLE system. The new system will provide many new features that will enhance the performance and reliability of the various databases. This project will also provide support for the addition of new functions for enhancement of existing systems. A significant effort will be to support the new in vivo screening effort. This contract would be responsible for the modification of the existing protocols and, as new requirements arise, the design and development of new programs to support these efforts. It is anticipated that new in vivo models will be developed and computer support will be required. Examples of these new models include microcapillary tubing assays and the plasma bioassay test. To support preclinical studies for the Decision Network Committee, the contractor would also be responsible for development of data query and reporting systems for in vivo data.

This project will support automation of the operations of the in vivo laboratory. Examples of this effort include integration of digital scales and calipers for tumor measurement. It will include automatic data entry, upload, and verification procedures. The project will continue distribution of DTP computer processing to high-speed workstations and personal computers. A semi-automated system will be developed to produce material safety data sheets. The database will contain safety data for a number of substances identified as toxic at several stages of the screening process.

Selective Acquisition of Compounds for Anticancer and Anti-AIDS Screening. Recompetition of a contract held by Starks Associates Inc. Estimated annual amount: $850,000 (50% cancer;

50% AIDS); total $4.25 million over five years.

The fundamental responsibility of the Drug Synthesis and Chemistry Branch (DS&CB) of the Developmental Therapeutics Program (DTP) is the acquisition of a large number of selected novel synthetic and characterized natural product compounds for evaluation as potential anticancer and anti-HIV agents.

The focus of this contract is the active solicitation, acquisition, and management of approximately 10,000 compounds per year of diverse structural and biological types. These compounds are selected by DS&CB from a much larger pool of available materials (12,000 to 15,000) identified by the contractor through extensive liaison with industry, universities, research institutes, government agencies, etc., and through the surveillance of the worldwide scientific literature. Reacquisition, i.e., the acquisition of samples previously tested for which larger quantities are needed for secondary evaluation, is also one of the responsibilities of this contract.

In addition, this contract is responsible for all the acquisition-related documentation tasks for new compound assignments and refill samples. These activities include entering the structures and related information for all the compounds acquired for testing into the NCI Drug Information System; checking all the information prior to NSC or sample number assignment; maintaining the accuracy of the chemistry database; handling the requests and receipt of refill samples; and microfilming all acquisition-related correspondence and records.

The interrelated liaison and documentation activities performed by the contractor have resulted in a sustained flow of chemical structures for selection by DS&CB personnel; the acquisition and registration of the necessary number of new compounds for testing; and the continued, significant participation of the academic community in the screening programs. During the first 3 years of the present contract (April 14, 1989 to April 13, 1992), the contractor (1) met with over 500 academic personnel at 135 universities and made liaison visits to 114 industrial firms, 5 research institutes, and 12 government agencies; (2) processed over 66,300 chemical structures from which DS&CB chose 38,700 for acquisition; and (3) performed the computer processing required for assigning NSC numbers to 26,694 selected compounds. These compounds, which are of diverse chemical structures and biological types, were acquired ex gratis from 1,773 suppliers; over 50 percent of the compounds were acquired from the academic community.

It is expected that the contractor will continue to ensure that approximately 10,000 compounds selected by DS&CB will be registered per year and that 200 to 400 of the registrations will be characterized natural products. The selected compounds will be chosen by DS&CB from 12,000 to 15,000 structures of available materials provided per year by the contractor. The contractor will be expected to reacquire additional quantities of compounds required for confirmatory and secondary in vivo evaluations.

Structures for selection and samples for testing from Europe are submitted to DTP through the NCI Liaison Office in Brussels. Approximately 10 to 15 percent of the annual input of 10,000 is received by this route. This contractor is responsible for the processing and registration of these compounds and for coordinating the supplier-related correspondence between NCI and the Brussels office.

The contractor will continually monitor the chemical and biological literature in order to provide a list of compounds from which DS&CB can select at least 3,000 each year for potential acquisition and testing in NCI's anticancer screen, anti-HIV screen, or both. This literature surveillance activity is also used to provide key publications relevant to topics of interest to DTP in the areas of cancer and AIDS chemotherapy.

The contractor will perform a number of specific tasks, such as (1) entering in the DIS all of the chemical structures along with specified nonstructural data for computerized selection by DS&CB; (2) acquiring samples of the selected compounds in quantities adequate for initial evaluation using a combination of methods, including field operations by the contractor and/or correspondence with potential suppliers; (3) reacquiring compounds of interest to the program; (4) registering the acquired compounds, both new submissions and refill samples, into the permanent chemical database; (5) maintaining the accuracy of the chemistry database; (6) providing complete correspondence and record-keeping services to maintain the overall DS&CB acquisition effort; and (7) utilizing a very broad base of past and current primary literature sources, published abstract services, and on-line information systems to continually monitor published works (including patents) in chemistry, biochemistry, and biology.

News Roundup

ODAC To Review Taxol NDA Nov. 16, Bristol, NCI To Discuss Pricing

FDA's Oncologic Drugs Advisory Committee will review the New Drug Application filed by Bristol-Myers Squibb Co. for taxol for treatment of refractory ovarian cancer at its next meeting scheduled for Nov. 16-17.

The taxol NDA will be discussed starting at 8 a.m. on Nov. 16 in conference rooms D and E of the Parklawn Building, 5600 Fishers Lane, Rockville, MD. The company filed the NDA for taxol last June.

NCI recently released taxol through its Group C mechanism for relapsed or refractory ovarian cancer and will expand the drug's availability for breast cancer through the Treatment Referral Center.

"Given the impressive clinical data for this compound and its very predictable and controllable toxicity, we expect a positive response from the NDA," NCI Div. of Cancer Treatment Director Chabner told the DCT Board of Scientific Counselors at its meeting this week.

Approval of taxol could be delayed by the requirement for an environmental impact statement, Chabner said. "Despite the fact that taxus bark collections have proceeded smoothly and to the satisfaction of all parties concerned, and despite the likelihood of an alternative resource being used in the near future, the environmental impact panel seems slow to appreciate that there will be no long term environmental impact," he said.

BMS officials have said that progress in synthesizing taxol precursors have progressed so rapidly that the company expects to be deriving its supply from synthesis, rather than the raw bark, in two years.

"The issue of a fair price for taxol remains to be resolved prior to marketing," Chabner said. "Our

agreement with BMS stipulates that the company will set a fair market price that will reflect the public investment in taxol research and development, as well as the level of patent protection and the complexity of producing the drug from limited supplies of natural materials.

"In initial discussions with BMS we asked them to consider the relative cost of comparable therapies, such as cisplatin, another grantee-discovered compound, which could serve as a benchmark for pricing this drug, and they have agreed to do so," Chabner said. NCI and BMS will reach agreement on pricing before taxol gets final approval.

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Paul Okunief, a radiotherapist from Massachusetts General Hospital, will head the Div. of Cancer Treatment's Radiation Oncology Branch starting next spring.

Okunief has published in the area of tumor physiology and has worked on the problem of applying magnetic resonance techniques to determining tumor oxygenation, blood flow, and metabolism in vivo, according to DCT Director Bruce Chabner. He will take the position in the NCI intramural program vacated last February by Eli Glatstein.

At the same time, Clinical Oncology Program Director Gregory Curt will create a new radiobiology branch in the COP, which will be headed by James Mitchell, who has been acting chief of the ROB since Glatstein's departure. The new branch, said Chabner, "will be a full partner in the laboratory training of clinical radiotherapy fellows, and will interact with each of the clinical branches in the development and support of new clinical protocols."

David Poplack, deputy chief of DCT's Pediatrics Branch, has accepted the position of chief of hematology-oncology at the Texas Children's Hospital in Houston and will be professor of pediatrics at Baylor Univ. School of Medicine. Poplack joined NCI 20 years ago as a clinical associate, and studied CNS penetration and intracerebral distribution of drugs.

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Percentage of American women over age 40 getting mammograms for breast cancer screening nearly doubled between 1987 and 1990, according to a new report from NCI.

Thirty-three percent reported having a screening mammogram in the previous year, compared with 17 percent in 1987, based on women's responses to questions about mammography from National Health Interview Surveys conducted in 1987 and 1990. Mammography screening among women with no regular source of health care increased from 6 percent to 15 percent.

The study was conducted by NCI's Nancy Breen and Larry Kessler. The National Health Interview Survey is conducted annually by the Centers for Disease Control.

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Lifetime probability of breast cancer among American women is about one in eight, according to a recent estimate by NCI and ACS researchers.

The estimate is higher than the one in nine figure reported earlier this year by the American Cancer Society, primarily due to the inclusion of the oldest age groups in the new estimate.

While the one in nine estimate used a cutoff age of 85 years, the new one in eight figure (approximately 12.6 percent) includes all age groups in five-year intervals up to an open-ended interval of 95 years and over. Each age interval is assigned a weight in the calculations based on the proportion of the population living to that age. The probability of developing breast cancer before age 85 is still one in nine.

NCI's Eric Feuer and Lap-Ming Wun, and Catherine Boring of the ACS, derived the new estimate using 1987-88 cancer incidence rates from NCI's Surveillance, Epidemiology & End Results Program. The work appears in summary in NCI's "Cancer Statistics Review 1973-1989."

The probabilities are based on population averages. An individual woman's risk may be higher or lower depending on factors such as family history or reproductive history.

"I thing there's been too much focus on this single number, the lifetime risk," Feuer said. "We don't know what incidence rates will be in the future, so it's something of a hypothetical number. Conditional probabilities (age-specific) over a decade or two are probably a better reflection of somebody's actual risk."

The researchers derived the following chart:

Chances of Developing Breast Cancer

By age 25: one in 19,608
By age 30: one in 2,525
By age 35: one in 622
By age 40: one in 217
By age 45: one in 93
By age 50: one in 50
By age 55: one in 33
By age 60: one in 24
By age 65: one in 17
By age 70: one in 14
By age 75: one in 11
By age 80: one in 10
By age 85: one in 9
Ever: one in 8