THE CANCER LETTER

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Oncologists Urge FDA To Allow Cancer Patients Access To Silicone Implants, But Continue Study

Oncologists and cancer patient organizations told an FDA advisory committee that silicone gel-filled breast implants should continue to be made available to women who have had a mastectomy, though more study of the safety of the devices may be required. "It is clear to me as a breast cancer physician and to my other colleagues who treat these patients, that the latest models of the breast prosthesis are as safe as current technology can produce, based upon current available scientific data," said Charles Balch, president of the Society of Surgical Oncology and board member of the American Society of Clinical Oncology. Balch,

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In Brief

Healy To Name Jay Moskowitz Deputy Director, Promote Mahoney To Deputy Budget Director

NIH DIRECTOR Bernadine Healy intends to name **Jay Moskowitz** NIH deputy director, though she has not made an official announcement yet. Moskowitz, associate director for science policy and legislation, has played a key role in development of the NIH strategic plan since the departure of former deputy director **William Raub** for the White House. He has been with NIH since 1969. Healy also plans to creat a new post of deputy director for management and budget and promote **John Mahoney** to fill it. Mahoney is currently associate director for administration. The promotions are awaiting higher-level review. Healy is recruiting for a new deputy director for intramural research. **Carl Kupfer,** director of the National Eye Institute, is serving as acting deputy. Remaining on Healy's immediate staff is **John Diggs,** deputy director for extramural research. . . . **MORTIMER BORTIN,** former scientific director and founder of the International Bone Marrow Transplant Registry based at Medical College of Wisconsin, was recently honored by colleagues at a gathering in Milwaukee. Bortin stepped down as scientific director last summer but continues to serve as the registry's principal investigator. **Mary Horowitz,** associate professor of medicine, was named the registry's new scientific director. The registry contains information on more than 14,000 transplants, about half of all those performed since 1970. . . . **THREE ONCOLOGY NURSES** are seeking the position of president-elect of the Oncology Nursing Society. The election result will be announced at the annual ONS meeting in San Diego in May. The candidates are **Linda Burnworth,** Columbus, OH; **Deborah Armstrong Houston,** Houston, TX; and **Sandra Lee Schafer,** Pittsburgh, PA.

Oncologists Tell FDA To Allow Use Of Silicone Implants For Mastectomy

(Continued from page 1)

chief of surgery at M.D. Anderson Cancer Center, also is an immunologist. "I urge you to allow this medical device to remain available to our patients, while all of us work together to perform definitive clinical and scientific studies."

FDA's General and Plastic Surgery Devices Panel was sympathetic to that view, and cited a special medical need for women with breast cancer. The panel recommended that FDA permit use of the implants under clinical protocols that would allow access to all women requiring reconstruction, but permit only limited trials to study women who choose the implants for augmentation purposes.

The advisory panel met Feb. 18-20 to hear testimony from doctors, companies and consumers on benefits and problems associated with the devices, which have been implanted in an estimated one million women. Each year, about 35,000 breast cancer patients have a breast implant.

The panel said there were insufficient data to reach a conclusion on the possible link between immune-related or connective tissue disorders and the implants.

[NCI's Div. of Cancer Etiology last fall announced it will release an RFP for a study of silicone implants in breast augmentation. The division's Board of Scientific Counselors gave concept approval to the study, estimated to cost $2.1 million over four years (**The Cancer Letter,** Nov. 22, 1991).

"We've met twice with FDA and said we would build in any questions that would be helpful to them," DCE Director Richard Adamson told **The Cancer Letter** this week. The study will enroll 12,000 women who already have the implants.]

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Balch testified that the results of a prospective clinical study at M.D. Anderson on the incidence of autoimmune disease and silicone leakage after implantation were negative. The study, done by Mark Schusterman, followed 592 patients who had reconstruction after mastectomy. Of those, 247 patients had 307 silicone gel implants. The others had an abdominal TRAM flap and served as a control group for the study.

The study's database was reviewed in early February to find out whether there were any reports of autoimmune disease. Schusterman and his staff contacted 90 percent of the patients who had not been seen in the last six months.

"Here are the results:" Balch said, "First, there were no instances of patients receiving silicone gel-filled prosthesis that had clinical or mammographic evidence of a broken implant. Second, only two patients among the 592 with breast reconstructive surgery later developed a documented autoimmune disease: lupus, and polymyalgia rheumatica. There were no patients with scleroderma." The patients with lupus had the TRAM flap.

The patient with symptoms of polymyalgia rheumatica was treated with a short course of low dose prednisone with complete remission. "If her silicone implant was contributing to her disease, one would predict that her symptoms would return if treatment was stopped," Balch said. "However, she has been off all therapy for a year and is doing well.

"Our analysis thus demonstrated that there have been no clustering of autoimmune abnormalities in our breast cancer patients with reconstructive surgery."

Balch also described a study at Memorial Sloan-Kettering Cancer Center, where surgeons have implanted over 1,100 silicone implants in the past 15 years. The recent survey of these patients by David Kinne and Ted Chaglassian found that MSK has no knowledge of any patient subsequently developing an autoimmune disease.

In addition, Balch said, John Woods at the Mayo Clinic has implanted more than 1,700 silicone prosthesis in breast cancer patients over 20 years, and has no knowledge of documented autoimmune disorders occurring in his patients.

"What is the scientific data demonstrating that silicone may induce an autoimmune or some form of immunological disease?" Balch asked. "While there are suggestions about this in the medical literature, the published reports are anecdotal in nature, each involving only a few patients, and the interpretations are inferential." Balch said he had reviewed the entire

published literature on the subject. "I cannot find any convincing studies which demonstrate an increased incidence of autoimmune disorders compared to a controlled population of patients. Nor are there any convincing immunological or clinical studies that demonstrate an immune response to silicone that may subsequently result in an autoimmune disorder."

The National Coalition for Cancer Survivorship asked FDA to consider that "the balance of risks and benefits associated with this product may differ" for breast cancer patients as opposed to women seeking breast augmentation. The group urged FDA to make the best information available to patients so they can make informed choices.

FDA Commissioner David Kessler pledged to make a decision on the implants within 60 days, by April 20. Kessler had called for a moratorium on distribution and use of the implants on Jan. 6.

The panel advised women who already have the implants to see their physicians regularly and, if an implant is found to have ruptured, to have it removed. Women with implants should follow established cancer screening recommendations, and it is especially important that women inform the mammography facility that they have implants, the panel said. Whenever possible, they should seek a facility accredited by the American College of Radiology.

FDA established a toll-free phone line to provide information on breast implants: 1-800-532-4440.

NCI To File Record Number Of INDs In 1992, Expanding Phase 1 Trials

NCI plans to file a record number of Investigational New Drug applications with the Food & Drug Administration this year, including 17 chemical entities and 36 new biologicals.

FDA is handling NCI INDs "expeditiously," according to NCI Div. of Cancer Treatment Director Bruce Chabner. "Our requests for help in dealing with problems are always met with cooperation and good advice, and in general cancer drugs are receiving a fair and expeditious hearing."

Of the 30 new chemical agents FDA approved in 1991, five were for cancer and one (ddI) for AIDS. Also, FDA approved two antibiotics for treatment of AIDS and cancer related infections (clarithromycin and foscarnet) and two biologicals (G-CSF and GM-CSF).

FDA Commissioner David Kessler told the National Cancer Advisory Board last month that the agency's oncology division is "a clean-desk operation"--there is no backlog of new drug applications (**The Cancer Letter**, Jan. 31).

"We do hope that NCI and the cancer research community will correct that situation by putting in more applications," Chabner told the DCT Board of Scientific Counselors last week. "And with the positive clinical results for taxol, anthrapyrazole, and the camptothecin analogs, we expect that subsequent years will be busy ones for FDA."

In conjunction with the increased number of IND filings, NCI plans to expand the number of institutions that are doing phase 1 investigations. DCT recently received 37 applications responding to an RFA for cooperative agreements for testing biologicals, Chabner said. "We plan to do the same thing with cancer drugs. We also plan to increase the number of phase 1 contracts this year," he said.

In addition, NCI has "mechanical ways" to increase the number of phase 1 investigators, Cancer Therapy Evaluation Program Director Michael Friedman told the board.

In the past, government restrictions on the amount of paper that can be mailed limited CTEP's ability to get the necessary information to institutions. Then, Friedman said, someone made a key discovery: "There's no limit on the number of phone calls." The institutions are getting their paperwork via fax machine.

At the next DCT board meeting, in June, CTEP will propose a new RFA that Friedman said will replace certain contracts for conducting phase 1 studies.

"There are a lot more people doing phase 1 studies than ever before and we want to increase this," Friedman said.

In addition to phase 1 treatment studies, there are an increasing number of phase 1 chemoprevention trials, noted DCT board member Paul Carbone. He said he would encourage Friedman to continue to have meetings with cancer centers to discuss treatment trials as well as some of the new prevention trials. "The NCI divisions which were set up 20 years ago just are not applicable today," Carbone said.

Chabner said DCT staff meets regularly with staff in the Div. of Cancer Prevention & Control to "break down barriers" between divisions. Sometimes the quickest way to test the activity of new anticancer agents is to test their efficacy in preventing second primary cancers, he said.

Effort To Increase Clinical R01s

Also at the next BSC meeting, Friedman will present data on the number of R01 applications submitted for clinical studies to the Experimental Therapeutics 2 study section.

NCI executives have been encouraging clinical investigators to submit their ideas as grant proposals

in order to create a "critical mass" of clinical applications, which traditionally have not fared well against basic science applications.

After two rounds of submission, the number of applications has about doubled from its usual level, Friedman said. By June, three rounds will have passed.

Just in the first two rounds, applications submitted in response to CTEP initiatives have doubled, from 13 to 26 (**The Cancer Letter,** Jan. 17).

"It looks positive; we have to see if the level will be sustained, and the number of grants actually funded," Friedman said last week. Though ET2 is "reviewing more applications than ever before, it is still not 100 percent clinical."

DCT Board Okays New Contracts For Production Of Natural Products

NCI's Developmental Therapeutics Program plans to fund the development of technology to produce large amounts of natural products tested as anticancer and anti-AIDS therapies through new contracts worth $3 million over five years.

The Div. of Cancer Treatment Board of Scientific Counselors last week gave concept approval for the new contracts, which would be let through master agreements.

In the past, large-scale production of drugs from plants or marine organisms was dependent on collection of biomass from the wild source, DTP Director Michael Grever explained. Examples include indicine N-oxide from Helotropium indicum, camptothecin from Camptoheca acuminata, and bryostatin from Bugula neritina.

However, NCI's experience with taxol showed that demands for a new agent can exceed the raw-material source, and alternative sources should be developed.

Last March, DTP organized a workshop to develop a new strategy for the large-scale production of natural products. Two key recommendations were the initiation of pilot-scale production studies when an agent enters preclinical development, and a major commitment to development of large-scale production technology when the agent passes enters phase 1 clinical trials.

The DCT board approved the new development strategy last June.

Following is the concept statement:

Master agreement for large-scale production of biomass for isolation of natural products. Proposed new RFP, $600,000 per year, five years, total $3 million; 50 percent cancer funding, 50 percent AIDS.

The mission of the Developmental Therapeutics Program is the discovery and development of novel agents for the treatment of cancer and AIDS. Natural products play an important role in the discovery process, and the function of this project will be to develop and apply efficient methods for the large-scale production of enough biomass to permit the isolation and purification of large quantities of active agents to meet program needs for the preclinical and clinical development of these agents.

The discovery of novel anti-HIV and anticancer natural product agents by the DTP Laboratory of Drug Discovery Research and Development and by other DTP-associated programs, such as the Natural Product National Cooperative Drug Discovery Group, requires that mechanisms for the large-scale production of these agents be established as soon as possible.

Phase One will involve the initiation of pilot-scale studies to explore the application of various techniques to the production of biomass for natural product agents entering preclinical development (decision point DN2A). The areas of study selected will vary depending on the agents being developed and might involve several relatively low-cost projects for each agent ($20,000-$50,000 per project).

Phase Two will involve the application of methodology developed in Phase One to the large-scale production of an agent entering clinical development (decision point 3). Since the best method(s) of production of an agent should have been determined in Phase One studies, substantial funding ($200,000-$300,000) can be devoted to applying the best production method(s).

The Request for Proposals (RFP) will be divided into a number of areas of activity: Large-Scale Recollections of a Specified Organism of Interest for Phase Two, Horticulture, Aquaculture, Plant Tissue Culture, Marine Organism Tissue Culture, Cultivation of Phototrophic Microorganisms, Cultivation of Nonphototropic Microorganisms, Genetic Engineering, Improved Analytical Procedures (Phase One only), Improved Isolation Procedures (Phase One only; a separate MA is in place for the large-scale isolation of natural products.)

Work areas for the development of improved analytical and isolation procedures have been included, but will only be incorporated in Phase One. The analytical and isolation procedures for the original discovery and isolation of a new agent might not be optimal, and improved procedures could be investigated prior to proceeding to large-scale production.

Offerors will be invited to submit proposals in one or more of the work areas included in Phases One and Two, with the option of restricting themselves to either one of the phases depending on their capabilities. In this way multiple pools of MA Holders with expertise in the different work areas in both phases will be established. As agents are approved by the Decision Network Committee, Master Agreement Order (MAO) RFPs will be issued for the appropriate work areas; the MAO RFPs will specify details of the particular tasks to be performed, and MAO contracts will be awarded to those MA Holders submitting the most acceptable proposals.

The board also gave concept approval to the following project that was moved from DTP to the Cancer Therapy Evaluation Program:

Storage and distribution of clinical drugs. Recompetition of a contract held by ERC Bioservices Corp, $1.8 million per year, four years; total $7.2 million.

This contract provides for the receipt, storage, dispensing, and distribution of investigational chemical and biological products used in NCI sponsored clinical trials. Large shipments of many

thousands of units of drugs are received from manufacturers and packagers throughout the world and are inspected on arrival. Frequently, relabeling or application of supplemental labels is necessary to meet FDA and NCI guidelines for completeness and clarity of labeling. Drugs are stored and inventoried in a large, secure, fire-protected warehouse under specified temperature conditions; at any one time, approximately 600,000 units (vials, ampules, bottles of tablets, etc.) are on hand in the repository.

Upon receipt of an approved Clinical Drug Request from NCI, repository staff repackage the specified amount of each drug in such a way that the shipment will reach the clinical center in good condition. Dry ice shipments, wet ice shipments, rush deliveries and emergency shipments are often necessary, and shipments are made to investigators throughout the US and the world. Computerized recordkeeping accompanies each step of the receipt, storage, and distribution of drugs. The contractor meets all applicable FDA Current Good Manufacturing Practices Regulations; since unused drugs returned from clinical sites must be disposed of as toxic waste, the contractor also possesses the necessary federal, state and local permits for generation and transportation of toxic waste.

In addition, this contract effort provides pharmaceutical support for randomized double-blind clinical trials. Since December 1989, the contractor has dispensed patient-specific, blinded bottles of study medication from open-label flutamide and placebo which is supplied by the manufacturer. In early 1991, ICI Pharmaceuticals Group agreed to supply tamoxifen and matching placebo tablets for three new breast cancer studies coordinated by the National Surgical Adjuvant Breast and Bowel Project. Two of the studies (NSABP B-23 and B-24), looking at adjuvant treatment of breast cancer, were initiated in May 1991 and are expected to enroll a total of 4,000 women; the third study, NSABP P-1, is a large, breast cancer prevention study which is expected to enroll 16,000 women beginning in January 1992. The manufacturer supplies the tamoxifen and placebo in unlabeled bottles, and NCI (through this contractor) provides the storage, patient-specific blinded labeling, and distribution to individual clinical sites.

In total, the three tamoxifen studies will require storage, label generation, labeling, dispensing, computerized record-keeping, and shipment of up to 400,000 individually labeled bottles of study medication. Dispensing for another double-blind chemoprevention study of isotretinoin vs. placebo in 1,080 patients at high risk of second primary tumors in non-small cell lung cancer, scheduled to begin early in 1992, will also be supported by this contract.

Accomplishments: This contractor has received, stored, shipped, and maintained records on hundreds of different drugs and dosage forms, and has maintained a nearly error-free record. 1991, a total of 27,476 shipments, comprised of 39,492 separate drug orders, were made; as of January 1992, the contractor processed approximately 120 shipments per day, an increase of 85% over the 1989 workload. Orders are shipped in a timely fashion, in most cases the same day they are received at the repository. Many orders for open-label drugs require study-specific inventory control, which requires substantial professional judgment and discretion from staff members. From May to December 1991, 14,250 blinded study bottles were dispensed, and the number of bottles required is expected to increase dramatically in 1992. Contract staff have met heavy workload demands and many nonroutine requests, and have performed admirably in implementing new project requirements, such as dispensing for tamoxifen studies, within tight time frames.

Future Plans: The effort required to support the three blinded tamoxifen studies, in addition to heavy workload of storage and distribution activities, has caused a marked acceleration in the expenditure of labor hours in the current contract; the level of effort, which was intended to last for five years, will be exhausted in July 1993 (approximately three years from the contract's inception). With this recompetition, it is hoped that a realistic level of effort has been anticipated and the resources in the contract will be sufficient for a full five years.

NCCR Honors Cancer Program Founders And Cancer Survivors

The National Coalition for Cancer Research honored cancer research advocates and cancer survivors at a recent awards dinner in Washington to celebrate the 20th anniversary of the National Cancer Act.

The Coalition presented Special Achievement Awards to President's Cancer Panel Chairman Harold Freeman and HHS Secretary Louis Sullivan and Outstanding Public Advocates awards to two cancer survivors, Marilyn Quayle and Brandon Tartikoff, former president of NBC Entertainment. Lilly Tartikoff received the award for her husband.

Freeman said the war on cancer must become "a ground war" in communities around the country and remove barriers to treatment of the poor. "We have a great responsibility to extend care to all Americans with cancer regardless of their ability to pay," he said.

Founders Awards for those who played leading roles in the drafting and passage of the National Cancer Act were presented to Sen. Edward Kennedy (D-MA), who guided Senate passage of the Act; Mary Lasker, founder of the Citizens Committee for the Conquest of Cancer; former Congressman Paul Rogers; former Senator Ralph Yarborough, who appointed a panel of experts to report on the needs for a national cancer research effort; and Benno Schmidt, who served as chairman of the Panel of Consultants, which drafted the framework for the Cancer Act, and later served as chairman of the President's Cancer Panel.

"There are a number of men and women who remember it was not always a celebration," Kennedy said. "Some remember the three editorials in 'The New York Times' condemning this effort, and the great struggle in the biomedical community."

Seven weeks after the Act was passed, Kennedy said, he asked a doctor to look at a bump on his son Teddy's leg. Teddy, then 12, was diagnosed with osteosarcoma.

"I'm a great believer in the work done by NCI, a great believer in it," Kennedy said. "I hear the critics saying, 'Why hasn't there been much progress?' Mary Lasker said it best: the greatest headline any of us will ever read in our lifetime is, 'Cancer Has Been Cured.'"

Schmidt recalled that when opposition to the Act was high, Schmidt became concerned about the political ramifications for Kennedy. "He said, 'Benno, do you still think the Act is the right thing to do?' I said, 'Yes.' He said, 'Then why don't you just devote yourself to getting the Act passed, and you let me worry about my politics.'"

Lasker and Yarborough were unable to attend. Lasker's sister Alice Fordyce, executive director of the Albert and Mary Lasker Foundation, received the award on her behalf. Yarborough's daughter in law, Ann Yarborough, said the former senator stayed home on advice of his doctor.

Congressional Awards went to Rep. Joseph Early (D-MA) and Sen. Ernest Hollings (D-SC), who introduced the amendment last year that gave NCI $160 million more than had been proposed in the Senate's appropriations bill.

The Coalition gave corporate awards to Bristol-Myers Squibb and Glaxo Inc. NCI Director Samuel Broder received a recognition award on behalf of NCI.

Broder said "one of the most unique opportunities" he has had as NCI director was to see adults who were treated for cancer as children testify at a Congressional hearing last summer commemorating the Act, with their own children in tow. "To Congress, I promise we will continue our work, and to the public, I promise we will not let you down," he said.

The Coalition also honored Eppie Lederer ("Ann Landers"), former House speaker Thomas (Tip) O'Neill, and former Surgeon General Everett Koop, although they were unable to attend the event.

More than 350 attended the event, held in Washington's Union Station on Feb. 18. Following a short film about the Act, there was a candlelight procession of cancer survivors who were present at the Act's signing by Richard Nixon on Dec. 23, 1971.

DES Exposure Studies Below Payline; NCI Considers Establishing Contracts

NCI is considering supporting studies of the long term health effects of diethylstilbestrol (DES) through new contracts because grant-supported studies have received low priority scores in recent years, an Institute executive told the National Cancer Advisory Board at its recent meeting.

NCI has supported studies of several cohorts of DES exposed women and their children since 1972, according to Iris Obrams, chief of the Extramural Programs Branch in the Epidemiology & Biostatistics Program, Div. of Cancer Etiology. DES is the synthetic estrogen promoted in the late 1940s and used until 1971 for prevention of miscarriages and pre-term births.

NCI has supported studies at Univ. of Chicago, Boston Univ. and the Mayo Foundation. In the last three years, these projects have received priority scores well below the funding range, and NCI has made special exceptions in order to keep these projects going, Obrams said.

NCI in collaboration with the NIH Office of Research on Women's Health, the Institute of Child Health & Human Development, and the Institute of Environmental Health Sciences, will sponsor a workshop to review data on long term health effects of DES exposure and make recommendations for future research. The workshop will be held at the Hunt Valley Inn, Hunt Valley, MD, on April 22-24.

Prior to the public meeting, NCI will meet with the investigators on the DES grant-supported projects. "We will seek consensus as to how continued followup of these mothers and their children is most likely to be assured. In the event that no grant application is to be submitted, the Div. of Cancer Etiology will support these cohorts by contract." Obrams said. "NCI remains committed to continuing its involvement in epidemiologic studies of DES."

The Chicago studies include about 1,500 mothers, of whom half were exposed to DES during their pregnancies, and their 800 daughters. The studies seek to determine the incidence of breast cancer and other diseases in these women. "Although NCI provided grant support to the Chicago cohorts by funding this research as an exception on several occasions, starting in 1972, the most recent grant application from the Univ. of Chicago in 1989 fell well outside the funding range," Obrams said. Support for the study is provided by a contract with NIEHS.

The Boston Univ. studies address breast cancer risks among 5,000 mothers, half of whom were exposed to DES. Obrams said NCI support for the project was specially extended last year.

The Mayo Foundation is conducting the multicenter National Cooperative DES Adenosis Project (DESAD), a cohort of 5,000 daughters, of whom 4,000 were exposed to DES. The project was begun in 1974 under an NCI contract. "This project has always been of great importance to the DES exposed women and their children, and has been a major souce of mostly reassuring data," Obrams said. The project was reactivated under grant support in 1984, but the most recent application for continuation, reviewed in 1989, received a priority score well outside the funding range, Obrams said.

"NCI has provided supplemental funding to this

grant, and NCI staff repeatedly, both in writing and by telephone, encouraged the DESAD investigators to revise and resubmit their application for continuation."

Between 1948 and 1971, an estimated 9 million children were exposed in utero to DES, representing 13 percent of all full term pregnancies during those years, according to Ruth Ann Giusti, special assistant for clinical affairs to NCI Div. of Cancer Treatment Director Bruce Chabner. Giusti reviewed the history of DES studies for the Board.

In 1971, Peter Greenwald, who later became director of NCI's Div. of Cancer Prevention & Control, reported the association between exposure to DES in utero and the development of clear cell adenocarcinoma of the vagina in young women. DES was banned for use in pregnancy that year.

"Followup of daughters of women who received DES during pregnancy suggests that while the risk of clear cell adenocarcinoma of the vagina is low, an estimated one per 1,000 women exposed in utero, epithelial changes in the cervix and vagina as revealed by colposcopy can be demonstrated in 65-90 percent of women and vaginal adenosis in 30-70 percent," Giusti said in her report.

"However, reported rates of cervical and vaginal intraepithelial neoplasia vary widely. While the rate of progression from vaginal adenosis to dysplasia and carcinoma in situ remains unclear, one study reported a twofold increase for dysplasia and CIS of the cervix and vagina among women exposed in utero to DES compared to a matched control group. No studies have yet shown an increased incidence of invasive squamous carcinoma of the cervix among DES exposed women. Mothers prescribed DES during pregnancy have been found to have a small increased risk of breast cancer with a relative risk of 1.4 with 20 years of followup. No clear evidence of increased cancer risk has been demonstrated in men exposed in utero to DES."

Giusti continued: "Developmental exposure to DES also has been associated with various abnormalities of the uterus, cervix and upper vagina which have been reported in 25-40 percent of exposed daughters. Inconclusive evidence suggests increased primary infertility in these women, rates of spontaneous abortion, ectopic pregnancy and premature labor are increased. A threefold increase in genital tract abnormalities has been reported among men with developmental exposure to DES including cryptorchidism and hypoplastic testes with unconfirmed reports of decreased fertility among these men. Additionally, animal studies have raised questions about immunologic effects of developmental DES exposure."

RFP Available For Development Of Cancer Risk Scale For ICCCR

The International Council for Coordinating Cancer Research announces the availability of funding to develop a comprehensive cancer risk scale for use by the general public, the media and the scientific and medical community.

ICCCR is a non-profit organization that encourages collaboration between cancer research scientists worldwide in an effort to accelerate methods to control cancer. The ICCCR Board of Directors has made a major commitment to devote resources of the organization to the crucial priorities in the area of prevention. The development of a comprehensive cancer risk scale is in response to recommendations made by a group of international specialists in cancer prevention and research at the ICCCR/NCI sponsored conference the "First International ICCCR/NCI Conference on Cancer Prevention: "Facts, Maybes and Rumors."

Following is the text of the RFP:

Purpose: The International Council for Coordinating Cancer Research (ICCCR) is seeking creative cancer specialists to develop a useful tool that will accurately and responsibly assess cancer risks. A comprehensive risk scale should identify and evaluate lifestyle, environmental, and hereditary risk factors and assign them a predictive rating for predisposition to an entire range of cancers. The goal of this undertaking is to provide concrete documentation, based upon scientific evidence of the risks of cancer. This information is critically important for the public to provide a sense of balance and priority in integrating cancer prevention measures into their daily living.

Background and Objectives: The ICCCR is acutely aware of the proliferation of cancer risk factors, real and perceived. Hardly a day goes by that the media is not alerting the public to yet another cancer causing substance. Many Americans have become convinced that "everything causes cancer" leading to confusion about constructive lifestyle changes that should occur to decrease the risk of cancer.

The role of lifestyle factors in the development of cancer has become increasingly evident as our knowledge about the prevention and development of cancer has evolved and become more sophisticated. Numerous studies have demonstrated that the most important factors for cancer risk are tobacco, alcohol, diet and undue exposure to solar radiation. However, there is a need to place this information in a balanced scheme and provide perspective as to how these relate to some of the other variables that have been

suspected including: radon, pesticides, PCBs, decaffeinating chemicals, electromagnetic fields, nitrites, chemicals in hair dye, and artificial sweeteners to name but a few.

Unfortunately, in decreasing their cancer risk, the public finds it easier to avoid eating apples due to possible contamination with alar than to reconfiguring their dietary habits to eat a low fat diet. A risk scale that will quantify the relative importance of each of these variables is critical to effectively empower the American public to take crucial steps in cancer prevention.

Further, there is no standard for the media to utilize in reporting known, suspected and alleged causes of cancer; standards that should be used to distill for the American public the real and potential risk of a specific chemical, food, or environmental exposure. Media must be enlisted as a responsible ally in efforts to educate the American public in the real and potential causes of cancer. In order to provide that service, the medical and research community must assist the media by quantifying what is likely to make the biggest differences in cancer risk, particularly those factors that are in the control of the individual.

Eligibility: Applications may be submitted by public or private, non-profit organizations such as universities, colleges, research institutions or independent advocacy organizations with expertise in the area of cancer prevention. Further the principle investigator must have a broad understanding of cancer prevention as evidenced by previous research, publications and/or appointment to prominent scientific advisory committees in the area of prevention and/or behavioral research.

All applications should be in English.

Award Criteria: Applications will compete for available funds with all other approved applications. The following will be considered in making funding decisions:

--Quality of project as determined by peer review

--Availability of funds

Support is available for up to a two-year period at which time it is expected that the project will be completed.

Application Procedure: Original application and 9 copies are due to the ICCCR by Tuesday, September 1, 1992. A letter of intent is requested by Wednesday, July 1, 1992.

Applications will be submitted to the Scientific Advisory Board for peer review. Criteria for scientific/technical merit review will include the following: scientific and technical significance; appropriateness of methodology for developing the risk scale; feasibility of the proposed development plan; and qualifications of the Principal Investigator.

Applications should include, but are not limited to:

A. Face sheet form (provided).

B. Table of contents.

C. Detailed budget for entire length of project.

D. Biographical sketch of principal investigator and any collaborators, including education, professional experience, honors and professional societies.

E. Publications--listed in chronological order. Accompany application with publications directly related to this project.

F. Research plan.

Letters of intent, applications and inquiries regarding the project should be sent to: Ann Denn O'Neill, International Council for Coordinating Cancer Research, 555 Madison Avenue, Suite 2900, New York, New York 10022, phone 212/319-6920, fax 212/371-1957.

RFA Available

RFA CA-92-06

Title: Intermediate endpoints and their modulation by chemopreventive agents

Letter of Intent Receipt Date: March 25

Application Receipt Date: May 19

NCI's Div. of Cancer Prevention & Control invites applications for cooperative agreements to support clinical trials which are directed toward examining the role of various chemopreventive agents and/or diet in the prevention of cancer. Applications may be submitted by domestic and foreign for profit and nonprofit organizations, units of state or local governments, and eligible agencies of the federal government. Applications from minority individuals and women are encouraged.

This RFA will use the NIH cooperative agreement (U01), for which substantial programmatic staff involvement of the awarding component is expected. The recipients will have primary responsibility for the development and performance of the activity. However, there will be government involvement with regard to 1) assistance securing Investigational New Drug approval from FDA, 2) monitoring of safety and toxicity, 3) coordination and assistance in obtaining the chemopreventive agent, and 4) quality assurance with regard to the clinical chemistry aspects of the study. The total project period may not exceed five years.

Approximately $1.5 million in total costs per year for five years will be committed. Three to five awards will be made.

The objective is to encourage cancer chemoprevention clinical trials that use biochemical and/or biological markers to identify populations at risk for cancer and/or to provide intermediate endpoints that may predict later reduction in cancer incidence rates. These studies may be developed in phases, including a pilot phase, that could proceed to full scale intervention. The main emphasis should be on small, efficient studies aimed at improving future research designs of chemoprevention trials, providing biologic understanding of what is happening in the trials, or providing better, more quantitative, and more efficient endpoints for these trials. After successful completion of the pilot phase (i.e., demonstrated modulation of marker endpoints by the intervention), subsequent studies can include phase 3 clinical trials involving the designated agent, the utilization of the monitoring test system, and a cancer incidence or mortality endpoint.

Investigators may apply at this time for the pilot phase or both phases.

Letter of intent may be sent to, and complete copies of the RFA received from Dr. Marjorie Perloff, Chemoprevention Branch, NCI, Executive Plaza North Suite 201, 9000 Rockville Pike, Bethesda, MD 20892-4200, phone 301/496-8563.