THE CANCER LETTER

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

Vol. 15 No. 38
Oct. 6, 1989

Price $185 Per Year North America
$200 Per Year Elsewhere

Broder Issues Clinical Alert On 5-FU/Levamisole Survival Advantage For Dukes C Colon Cancer

NCI this week issued a clinical alert to inform physicians about the survival advantage offered by 5-fluorouracil and levamisole for the adjuvant therapy of Dukes C colon cancer.
(Continued to page 2)

In Brief

Carbone To Give Up ECOG Chairmanship; DCE's Adamson Receives Presidential Executive Award

PAUL CARBONE plans to resign as chairman of the Eastern Cooperative Oncology Group within the next year, he recently informed group members. He has headed ECOG since 1970 and has seen it grow from about 800 patients a year on 12 protocols to 6,000 patients a year on 100 protocols. "After 20 years, it's time to get someone else involved," he told The Cancer Letter. "I'm 58, and I've got other things I would like to do." Carbone is director of the Univ. of Wisconsin Clinical Cancer Center. . . . **DCE DIRECTOR** Richard Adamson has received the 1989 Presidential Meritorious Executive Rank Award at Constitution Hall. President Bush was there to congratulate the winners. . . . **LOUISE BRINTON,** chief of the Environmental Studies Section in the Environmental Epidemiology Branch of the Div. of Cancer Etiology, has been named president elect of the Society for Epidemiologic Research. . . **JOSEPH STEINER** Cancer Prize will be awarded next month to Isaiha (Josh Fidler), at M.D. Anderson, and Lance Liotta, chief of the Laboratory of Pathology in the Div. of Cancer Biology & Diagnosis. Each will receive $114,250 in research support. . . . **MICHAEL HAWKINS,** chief of the, Investigational Drug Branch in the Div. of Cancer Treatment, will receive the NIH Equal Employment Opportunity Award this month. . . . **CORRECTION:** National Cancer Advisory Board's vote against the Dietary Fat Intervention Trial in closed session was 9-3, not 6-3 as reported in last week's issue. The proposal's percentile score of 13.2 was assigned by computer, not by the special study section. In proposals that are reviewed by special study sections, the priority score is the better indicator of fundability. As was reported, the proposal had a priority score of 152. . . . . **SIXTH INTERNATIONAL** Conference on Adjuvant Therapy of Cancer, March 7-10, 1990, will accept abstract submissions until Dec. 1. For abstract forms and copies of the preliminary program, contact Mary Humphrey, Conference Coordinator, Arizona Cancer Center, Tucson, AZ 85724, phone 602/626-2276 or FAX 602/626-2284.

Dukes C Patients Should Be Offered 5-FU/Levamisole, NCI Alert Says

(Continued from page 1)

For Dukes C patients, the combination reduces the risk of dying of recurrent colon cancer by one third, the alert said.

The release of the clinical alert closely follows the decision to end untreated control arms in NCI sponsored trials involving Dukes C colon cancer (**The Cancer Letter**, Sept. 22). It also coincides with publication of the results of the North Central Cancer Treatment Group's study of colon cancer therapy in the October issue of "The Journal of Clinical Oncology."

The alert was mailed to 35,000 doctors, directors of institutions accredited by the American College of Surgeons, directors of NCI funded cancer centers and principal investigators of NCI's Community Clinical Oncology Program.

"NCI believes that levamisole and 5-FU is an option that should be discussed with nearly every patient found to have colon cancer with nodal involvement (Dukes C)," the alert said. Patients in trials who were randomized during the past few weeks to observation only arms are being told they might benefit from adjuvant therapy.

The decision to issue the alert was made because of the dramatic potential of the therapy to save lives, said NCI Director Samuel Broder. "This combination is something every physician and surgeon should be aware of," he said at a press conference to release the clinical alert.

Broder recommended that patients with Dukes C colon cancer strongly consider enrolling in an NCI sponsored clinical trial, and to discuss treatment options with their physician.

THE CANCER LETTER

Editor: Jerry D. Boyd
Associate Editors:
Patricia Williams, Kirsten Boyd Goldberg

P.O. Box 15189, Washington DC 20003
Telephone (202) 543-7665
FAX No. (202) 543-6879

Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS update. (ISSN 096-3917)

This year, there will be about 110,000 new cases of colon cancer in the U.S., and about 21,000 of these patients will have regional lymph node involvement at the time of surgery, according to the alert.

Five year survival rates for Dukes C patients is about 30 to 40 percent, compared to 60 to 70 percent for patients who have local tumor without positive lymph nodes.

"Any (Dukes C) patient with a high risk of recurrence is getting short shrift if he is not offered the option of levamisole/5-FU," said Charles Moertel of Mayo Comprehensive Cancer Center and chairman of the NCCTG, who was at the press conference. "Patients can get the treatment, close to home, by community physicians."

The NCCTG study, which was reported at the American Society of Clinical Oncology meeting two years ago, found a significant disease free survival advantage in the combination arm for Dukes C patients, and a lesser advantage for Dukes B_2 patients.

Final publication of the results were delayed two years so that patients could be followed longer, Moertel said. The 408 patients now have been followed for five to 11 years.

The study found that compared to the surgery only control, the combination of 5-FU/levamisole produced a highly significant reduction in tumor recurrence ($p=0.003$) as well as a delay in recurrence. An overall survival improvement was not clearly demonstrated. Results with levamisole alone following surgery were better than surgery alone but inferior to the combination therapy.

To confirm the results, NCI sponsored a larger intergroup study conducted by the Eastern Cooperative Oncology Group, Southwest Oncology Group and NCCTG. Accrual of 1,296 patients was begun in March 1984 and completed in October 1987. The data were analyzed at predetermined intervals, most recently on Sept. 1.

Complete results of the intergroup study have not been made available. The results will soon be submitted for publication, Moertel said.

According to the clinical alert, "This intergroup study prospectively separated the analysis of Dukes B and Dukes C patients. It has confirmed the efficacy of levamisole and 5-FU for Dukes C patients; the impact on recurrence rates, disease free and overall survival were clinically substantial and highly statistically significant. Patients in the

levamisole and 5-FU group experienced a reduction in the rate of recurrences and death of at least one third. Their survival benefit was of similar magnitude to that observed in the preliminary trial (approximately 12 percentage points). Side effects were generally mild, although a single toxic death did occur.

"An advantage was not seen for treatment with levamisole alone. In the Dukes B patients the followup information is insufficient to permit statistically valid comparisons. These data are being closely monitored since the median followup is only three years."

The therapy should be started no later that three to five weeks after surgery, and should continue for one year, he said.

Moertel said the reason the data on Dukes B patients is at this point unclear is the lack of large numbers of Dukes B patients on trial. "We don't have these patients coming in as often, and it is important to be sure that adjuvant therapy has a significant effect because these patients will have a 75 percent chance of 5 year survival without any further treatment," he said.

Levamisole, used for deworming animals for the past 20 years, is commercially available for veterinary purposes but not for human use. It was placed on Group C status in May. The manufacturer, Janssen Pharmaceutica, is expected to submit a new drug application to FDA soon.

Until then, physicians treating patients who cannot enroll in clinical trials can obtain levamisole and a document describing dosage and monitoring free of charge by registering patients through the Drug Management & Authorization Section of the Investigational Drug Branch in the Cancer Therapy Evaluation Program, phone 301/496-5725, between 9 a.m. and 5 p.m. Eastern time.

CTEP Associate Director Michael Friedman said 5-FU/levamisole can now be considered "standard care" for Dukes C patients. However, not all patients have been cured by the combination and many questions remain, including the best way to use 5-FU/levamisole.

"Continued entry of patients into clinical trials investigating other therapies is essential," Friedman said. Ways of biochemically modulating the combination with other agents are being explored in current trials, he said.

One major question is whether to treat Dukes C patients who had surgery months ago. "We don't know the best way to treat these patients or whether 5-FU/levamisole would help," Friedman said. "Current trials are studying that."

FDA Commissioner Frank Young called the combination "a major advance," and complemented Moertel and NCI for making the treatment advance known before publication.

In recent months, NCI officials have indicated they intend to use the clinical alert format more often to draw attention to important clinical results as necessary.

NCI Deputy Director Maryann Roper, at a conference on mammography last week, mentioned last year's clinical alert on breast cancer. "Our view is that keeping quiet about results before they are published is akin to insider trading."

Broder, who has been outspoken on the issue of faster publication of trial results, told the National Cancer Advisory Board at its recent meeting that the institute would issue a clinical alert on the treatment advance.

He told **The Cancer Letter** that he did not seek formal NCAB approval of the action, but did discuss the alert with surgeon groups and with John Niederhuber, chairman of the Div. of Cancer Treatment Board of Scientific Counselors.

Fox Departure End Of Era, At Least For Now, In Construction Program

Donald Fox will leave NCI Nov. 1, taking terminal leave before retiring from the Public Health Service Jan. 1, 1990. His departure will mark the end, at least for now and perhaps for years to come, of an era.

Fox has been chief of the Research Facilities Branch since May, 1973, when he succeeded George Jay. The branch, at that time in the Div. of Research Resources & Centers, the predecessor of the present Div. of Extramural Activities, had a budget of $33 million that year, most of which was awarded to cancer centers around the country in construction grants. The previous year, in the heady time immediately after passage of the National Cancer Act of 1971, the branch's budget was $44 million.

Although the decline in construction funds continued, dropping from $32 million in 1974 to $20 million in 1976 and to $11 million in 1980, the program continued to have a major impact on development and renovation of cancer research space. But in 1981, President Reagan's Office of Management & Budget set out to kill all federal support of biomedical research construction. Congress, which had overcome

reluctance of Presidents Nixon, Ford, and Carter to fund NCI grants for construction and renovation, caved in to Reagan and came up with only $2 million. That dwindled to $1 million in 1984, came back modestly to $5.5 million in 1985 when money originally appropriated and earmarked for construction of a cancer center at West Virginia Univ. was made available when the National Cancer Advisory Board disapproved the WVU application, and then dropped to zero three of the last four years. An appropriation of $2.5 million in 1987 went mostly for renovations at Frederick Cancer Research Center.

By any measurement, NCI's support of construction and renovation of cancer research facilities has to be considered one of the most successful of any of its extramural efforts. During the first years after the National Cancer Act, NCI required grantee institutions to provide 25 percent matching funds. That requirement was increased to 50 percent in 1978. Thus, the $220 million of NCI awards since 1972 resulted in development of at least $550 million worth of cancer research space.

That does not tell the whole story. Most of the grantees used their NCI money as leverage to raise more than the required matching funds, in some cases far more. The Univ. of Arizona took a $1 million grant and raised enough state and local money to build a $15 million cancer center. La Jolla Cancer Research Foundation, starting with a $600,000 NCI grant, built a $6 million facility. The Univ. of Southern California received $10 million in NCI money, developed a clinical and laboratory research center at a cost of about $50 million and is still raising money for further expansion which will probably double that investment.

In what may be the niftiest example of all, William Powers submitted an application for help in building a new radiation oncology center at Wayne State Univ. The grant received a good priority score but there was no money to fund it. However, Powers was able to use the existence of an NCI approved application and raised the $6.5 million he needed, without a dime of federal money.

Fox estimates that NCI's support has enabled development of about two million square feet of research space, an amount equivalent to total research space at the NIH campus.

"Many of the grants we awarded helped in development of what are now some of our largest established cancer centers," Fox said. "They were the cornerstone around which centers were built."

Congress declined to appropriate any money for the construction program in the 1988 fiscal year, citing a need for a panel of experts to consider all biomedical research facility needs. NIH convened a panel, which after a thorough review, determined that $2.5 to $3 billion in federal support would be required over seven years. Previous surveys, by the National Cancer Advisory Board more than 10 years ago, and a study financed by Armand Hammer and the American Cancer Society four years ago, determined that at minimum, NCI should make about $25 million a year in construction and renovation grants. The NCI bypass budget for FY 1991 calls for $55 million in construction.

Considering the program's undeniable success and the well documented needs, the reluctance of Congress and the White House to support it is incomprehensible.

"The biomedical research community sits now at a stage where the early programs we supported are in need of renovations, upgrading their mechanical systems, in need of meeting biohazard requirements, and have to meet new animal facility requirements," Fox said. "In terms of program development, new technology has added another dimension, a new range of needs. Twenty million dollars a year, which is modest from the federal perspective, probably would be sufficient to meet those needs, with the tremendous leverage available. The level of federal dollars is not as importance as the presence of a viable program."

Fox will join the Rockville, MD, firm of Maurice W. Perreault & Associates Inc. Nov. 1 as senior vice president for biomedical resources program and prearchitectural planning. He holds civil engineering degrees from Yale, master of public health degrees from the Univ. of Minnesota, and has a PhD in environmental health. Before joining NCI in 1972, he conducted research on the application of laminar flow technology to the hospital operating room environment, and spent three years with NASA "as planetary quarantine program officer." His job there was to assure that the Viking spacecraft, which made a soft landing on Mars in 1976, would not contaminate that planet with harmful material.

The NCI construction program will once again be viable, if the new division director responsible for it has anything to say.

"We certainly intend to keep the Research Facilities Branch intact for the time when funds become available," Alan Rabson, director of the Div. of Cancer Biology & Diagnosis, told **The Cancer Letter**. The branch has been moved from the Div. of Cancer Prevention & Control to DCBD, along with the Cancer Centers Branch, Organ Systems Coordinating Branch, and Cancer Training Branch.

Fox had previously lost most of his staff to transfers or retirement. When he leaves, only his secretary of three years, Taffene Dobson, will be left. But Rabson said that an acting chief of the branch would be named, and a permanent chief appointed once construction money is again available.

The four branches will be grouped under the new Centers, Training, & Resources Program. Brian Kimes, presently director of the Extramural Research Program in DCBD, will move over to head the new program, retaining his title as associate director of the division. A new AD will be recruited to head the Extramural Research Program, which includes the Cancer Biology, Cancer Diagnosis, and Cancer Immunology branches.

The Centers Branch is also without a chief, with the departure in July of Lucius Sinks. Rabson said that one of Kimes' first priorities when he returns from his temporary job as acting head of the new NIH Office of Scientific Integrity, will be to find a Centers Branch chief.

Andrew Chiarodo remains as chief of the Organ Systems Coordinating Branch, and Vincent Cairoli remains as chief of the Cancer Training Branch.

Three additional members who are involved with cancer centers will be named to the DCBD Board of Scientific Counselors. The board already has one member from a center, Vittorio Defendi, director of the New York Univ. Cancer Center.

In keeping with NCI Director Samuel Broder's determination to give centers more visibility, DCBD will be renamed to include "centers." Rabson said the new name had not yet been selected.

Bush Signs Continuing Resolution; Conferees To Meet On 1990 Budget

President Bush signed a continuing resolution last week that provides HHS, NCI and other federal government agencies with the same level of funding as last year until a conference committee can iron out differences in the appropriations bills passed by the House and Senate.

The conference committee was scheduled to meet Oct. 3 (past **The Cancer Letter's** deadline) to begin that process for the HHS appropriations.

Meanwhile, the Senate Appropriations Committee completed its markup of the FY 1990 budget and recommended an NCI appropriation of $1.67 billion, which is $16 million over the House recommendation and $22 million over the President's budget.

The committee's report on the appropriations bill said that funds to continue the same number of cancer centers core grants in FY 1990 as in FY 1989 were included.

"Cancer centers are an extremely valuable resource in NCI's comprehensive cancer program which perform basic cancer research, disseminate information, transfer technology and apply the latest scientific findings to their communities," the report said. "The committee urges NCI to explore innovative ways to strengthen the centers program to improve the accessibility to state of the art treatment for all Americans.

"The committee is well pleased with the study prepared on the subject of cancer centers by the Institute of Medicine." The report then lists some of the IOM report's findings, including the fact that, "scientists and clinicians in institutions with NCI core grants receive nearly one half the research project grants awarded by NCI through a process of competitive peer review. . . . and as a group, the centers are a valuable resource for NCI in the national effort to understand, prevent, and treat cancer and its consequences.

"Finally, the committee is concerned that in view of the important role played by cancer centers that five such centers may be defunded during fiscal year 1990. The committee has added funds to the NCI budget to help ensure that the number of cancer centers remains constant.

The bill also provides:

--$34 million for upgrading the NCI supercomputer.

--$4 million for NCI to increase the pediatric AIDS research effort.

--$96 million, a $900,000 increase over FY 1989, for NCI's information dissemination activities, including the Physician's Data Query.

--$12.5 million to match the $12.5 million raised by Armand Hammer's STOP Cancer

Foundation. The committee said the funds donated by the foundation are to be used "to provide support for cancer biology and adoptive cellular therapy as determined by the NCI director." The funds appropriated by the committee are to be allocated through the normal peer review process, the committee said.

--An unspecified amount to increase the research effort in retroviral research.

The committee also urged NCI to:

--Strengthen existing programs and develop new programs to address the high cancer mortality rates of minorities and persons over age 65.

--Make it a "significant priority" to target native Hawaiians and other Pacific islanders in educational campaigns to reduce the high cancer mortality rate of these populations.

--Review the need to develop a focused statistical series to examine the role agricultural chemicals may play as causative agents.

--Increase the emphasis on prevention research. The committee said it "recognizes that a nutrition and cancer research laboratory is invaluable to this effort."

--Report to the committee next year on efforts to increase enrollment in clinical trials, to speed up the rate at which new treatment or drugs are made available for general use, and to provide third party coverage for patient care costs for clinical trial participants.

Following is an update of recent action in Congress or recently introduced legislation.

Smoking And Tobacco

The Senate voted last month to ban smoking permanently on all domestic airline flights. The bill, part of the transportation appropriations package, was sponsored by Sen. Frank Lautenberg (D-NJ), a former two pack a day smoker. The House has approved legislation that makes the current ban on smoking on flights of two hours or less permanent, but does not extend it to all domestic flights. The differences between the bills must be resolved by a conference committee, and passed by both houses.

The conference committee was expected to meet late this week. Since most of the funding provisions targeted toward fighting illegal drugs were attached to the transportation bill, it may take several weeks for conferees to agree on the appropriations bill.

Other smoking bills introduced recently:

<>HR 1250, by Rep. Thomas Luken (D-OH), will permit only text advertising in newspapers, magazines, and billboards. The bill has been referred to the Transportation & Hazardous Materials Subcommittee.

At a subcommittee hearing on the bill recently, Luken said that, "The merchants of addiction" promote their products three ways, "first by spending lots of money; second, by repeatedly exposing young people to the insidious siren song linking sex and romance to smoking; third, by spreading their message in ways that do not appear even to be advertisements, such as paying to have cigarettes in the movies."

<>HR 3106, by Rep. Richard Durbin (D-IL), will cut off federal education block grants to elementary or secondary schools that permit tobacco products to be sold to or used by students on school property. The bill was referred to the House Education & Labor Committee.

<>S 1527, by Lautenberg, would provide incentive grants for states that enact legislation to limit youth access to cigarettes. It also includes provisions for a tax increase on cigarettes.

Cancer Screening

Several bills have been introduced in Congress that would repeal Medicare catastrophic coverage provisions. Some of the measures would have the effect of deleting coverage for mammography screening, which is scheduled to become effective in 1990.

Rep. Dan Rostenkowski (D-IL) last month introduced HR 3230, which would revise benefits and financing provided under the Medicare Catastrophic Coverage Act of 1988. A provision of the bill would retain the mammography screening benefits.

<>HR 3285, by Rep. Barbara Vucanovich (R-NV), to require state medicaid plans to provide coverage of screening mammography. Referred to the Committee on Energy & Commerce.

<>HCR 197, by Vucanovich, a concurrent resolution expressing the sense of Congress that each state should require health insurance providers to provide coverage for screening mammography in accordance with guidelines established by NCI.

Health Care Financing Administration has proposed regulations for the Medicare Catastrophic Coverage Act of 1988 that would set forth payment limitations and conditions of coverage of screening mammography.

For services furnished in 1990 the payment limit would be $50. The conditions would

consist of quality standards to assure the safety and accuracy of screening mammography services performed by qualified physicians and other suppliers.

Comments must be received before Oct. 31. Address: HCFA Attention: BERC-619-P. P.O. Box 26676, Baltimore, MD, 21207.

Other Legislation

Other legislation recently introduced:

<>HR 3251, by Rep. Mary Rose Oakar (D-OH), authorizes an additional $25 million appropriation for NCI to conduct research on breast cancer for the purpose of finding a vaccine.

<>HR 2601, by Rep. Henry Waxman (D-CA), establishes the Agency for Health Care Research and Policy within PHS, and would require evaluation of the effectiveness of health care services.

<>HR 751, by Frank Guarini (D-NJ), to suspend duty taxes on tamoxifen citrate for three years. (NCI designated tamoxifen as the adjuvant treatment for more than 60 percent of all breast cancer patients.) Tamoxifen is packaged in the U.S., but its ingredients are imported from England, where manufacturing is done for ICI Pharma, which has the exclusive right to sell the drug in the U.S. until 2002. The bill was referred to the Subcommittee on Trade.

<>HR 2989, Sen. Robert Kerrey (D-NE), a provision in the Treasury appropriation, provides $5 million in grants to the Eppley Institute for Research in Cancer and Allied Diseases in Nebraska. Funds will be used to build a six floor addition. Passed by the House and Senate.

Raise Cigarette Taxes To Fully Fund The Bypass Budget, NCAB Declares

The National Cancer Advisory Board has passed a resolution urging Congress to increase the federal excise tax on cigarettes by at least 20 cents and to use the tax collected to increase support for biomedical research, including full funding of the bypass budget.

The resolution notes that tobacco use is a major cause of morbidity and mortality due to cancer and other diseases, and that the adverse effects of tobacco use contributes to an increased need for research and for health care services.

"The National Cancer Advisory Board finds that the federal excise tax on cigarettes should be increased by at least 20 cents and that the monies collected through this tax should not be included in general revenues, but directed specifically to increased support for public and professional education to promote prevention and cessation of tobacco use; increase health care services, including prevention, diagnosis and treatment for those unable to pay for such services; and increased support for the conduct of biomedical research and training, including full funding of the bypass budget of the National Cancer Institute."

The NCAB received some criticism from longtime cancer program supporter Mary Lasker after an article in **The Cancer Letter** (Sept. 1) reported a debate at the May NCAB meeting in which some board members expressed doubt about the value of the bypass budget. After NCI Director Samuel Broder and others discussed the purpose and history of the document, however, the NCAB approved the 1991 version of the bypass budget.

In a Sept. 6 letter to NCAB Chairman David Korn, Lasker wrote: "Those of us who fought long and hard for the creation of the National Cancer Act did so because of our concerns that the ravages of this disease were not being appropriately addressed by our government. Funding was inadequate based upon the research potential which existed and hundreds of thousands of lives were being lost each year to a disease for which the government had no direction and no policy to manage.

"As a result, advocates joined forces with the leaders of this nation...endorsing the belief that specific Presidential authorities were necessary to address the growing cancer problem in this country. Among these authorities is the bypass budget....

"Because of the National Cancer Act, NCI is the only government agency that can honestly reflect to the President, the Congress and the American people the level of funding which is vital to maintain our crusade against cancer.

"The bypass budget is the conscience and voice of the cancer research community--on behalf of the American people. Why would anyone want to diminish this voice by creating a 'realistic budget' in line with the fiscal constraints of our economy?

"Instead of turning our backs on the priorities of our research potential and the needs of our National Cancer Program, perhaps we should turn our efforts to the inequities in the government that are creating this fiscal crisis."

Lasker wrote that the Dept. of Defense

spends more for research and development in two years than NIH has spent in the past 100 years. "Why should the research community fall into the trap of adjusting its priorities downward when the political realities are that the resources are available--they just are not being used to cure disease and disability.

"The road is tough right now--but it will crumble and disappear altogether if the research community fails to believe in itself, its mission, its scientific needs, its responsibility for advocacy and the benefits that medical research can bring to the American public."

Referring to the bypass budget, Lasker concluded: "Let it shine as a 'beacon of light' in the hopes that some day someone will have the courage and conviction to respond to its call."

John Ultmann, chairman of the National Coalition for Cancer Research, also wrote to Korn in support of the bypass budget. "Now, more than ever before, we need the bypass budget to represent a true reflection of what cancer research needs," Ultmann wrote. "Perhaps one day soon we will stand behind it and clamor in support of it in numbers so large that our presence can no longer be ignored."

In addition to the resolution, the NCAB wrote to Sen. Frank Lautenberg (D-NJ), to congratulate him on his success in incorporating a total ban on smoking on domestic flights in the transportation appropriations bill. "No one should be forced involuntarily to inhale the toxic components of cigarette smoke as the price of travelling by air," the board wrote.

Program Announcement

Title: Studies on cancer etiology in finfish and shellfish
Application Receipt Dates: Feb. 1, June 1, and Oct. 1, 1990

The NCI Div. of Cancer Etiology and the Extramural Program of the National Institute of Environmental Health Sciences invite grant applications through a joint program announcement for basic studies intended to provide insights and approaches to an understanding of the possible etiology of neoplasia in finfish and shellfish. This type of solicitation is used when it is desired to encourage investigator initiated research projects in areas of special programmatic interest to NIH. Applicants funded under the PA are supported through traditional research grants. Only research project (RO1) grant applications will be considered to be responsive to this PA.

Experimental evidence to date suggests that some fish species, when compared to rodents, are less sensitive to the toxic and more responsive to the carcinogenic effects of xenobiotics; they react more promptly, with a shorter latency period and with greater specificity. These characteristics suggest that they should serve as major indicators of agents in the environment which may pose a risk to humans. Not only are these aquatic animals obvious candidates to serve as sentinels of carcinogenic pollutants in the environment, but also the epizootics of cancer, which they experience in confined or circumscribed water areas such as lakes and canals, or sharply defined areas of rivers, bays and estuaries offer a natural experiment for establishing cause and effect relationships, interspecies comparisons, and for establishing target cells at risk.

An RFA for studies on the etiology of neoplasia in poikilothermic, aquatic animals: finfish and shellfish was issued in 1986. Fifty four applications were received in response to the RFA and a total of nine awards made.

The overall purpose of this PA is to accelerate the development of additional understanding relative to studies on the possible etiology of neoplasia in finfish and shellfish.

Consistent with the title of this PA area broad spectrum of studies that would greatly facilitate our understanding of the etiology of neoplasia in finfish and shellfish. Listed below are some commonly identified needs, but which are not intended as a comprehensive list of possibilities.

1. Evaluation of the similarity of metabolic function in procarcinogen activation among different species of invertebrates and/or vertebrates in regard to phase 1 and 2 reactions. Assessment of the role of fish hepatocytes in metabolism of procarcinogens. Studies on bioavailability and transfer of xenobiotics and their metabolites from invertebrates to fish and from invertebrates and fish to mammals.

2. Effects of environmental and physiological variables of water temperature, age, sex and gonadal development on bioavailability and metabolism of xenobiotics.

3. Development of in vitro culture systems for normal and neoplastic cells from invertebrates and vertebrates and analysis of adducts to macromolecules of environmentally relevant xenobiotic metabolites.

4. Studies on chemical/chemical and chemical/viral interactions in the etiology of aquatic animal neoplasms and the identification of oncogenes in invertebrate and vertebrate species.

5. Analysis of DNA repair capacity, mitotic index, sister chromatid exchange, cell cycle time and enzyme pathways for xenobiotic metabolism under various temperature conditions in poikilothermic aquatic animals and determination of the relationship to the persistence of genetic lesions that might lead to tumorigenesis.

6. Studies of factors involved in promotion or progression of a tumor in aquatic species. Assessment of transplantability of neoplasms.

7. The effect of chemical pollutants on the immune response in aquatic animals and the role of the immune system in aquatic animal neoplasia.

8. Expansion of the experimental oncology database on various promising fish species as carcinogen assay subjects. Tumor induction studies with chemical agents which utilize species such as the rainbow trout, the medaka or Japanese killifish, the guppy, the zebrafish, the sheepshead minnow, or other established models. Besides tumor induction, studies might include the further development of data on potency of carcinogenic agents in fishes, utilizing fish molecular, cellular and tissue responses with screening endpoints such as unscheduled DNA synthesis, liver enzyme induction, chromosomal aberrations, sister chromatid exchange or detection of altered foci in such target tissues as liver.

The total project period should not exceed five years. Nonprofit and for profit organizations and institutions, governments and their agencies and individuals are eligible.

Copies of the complete program announcement and additional information may be obtained from Dr. David Longfellow, chief, Chemical & Physical Carcinogenesis Branch, DCE, NCI, Executive Plaza North Suite 700, 6130 Executive Blvd., Rockville, MD 20892; phone 301/496-5471.

NCI CONTRACT AWARDS

Title: Evaluation of the 1990 Medicare legislation on mammography usage in the NCI Mammography Consortium.
Contractor: Mathematica Policy Research Inc., $376,238.

Title: Provision, maintenance and transfer of tumor bearing laboratory animal models for investigation.
Contractor: Laboratory Animal Services Inc., $2,621,155.