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Senate Committee Approves $1.74 Billion For NCI, Seeks Activation Of Dietary Intervention Trial

The Senate Appropriations Committee last week approved a spending bill that provides $1.747 billion for NCI in FY 1991, a 6.9 percent increase over FY 1990, and $53.4 million above the Administration request. The Senate amount came in stark contrast to the figure approved by the House Appropriations Committee back in July, which

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In Brief

NCAB To Protest Tobacco Ads In 'Family Circle'; ACS Petitions For Taxol Source Designation

"FAMILY CIRCLE" magazine will soon be getting a letter from the National Cancer Advisory Board objecting to the heavy schedule of cigarette advertising it carries. "That's a scandal," NCAB Chairman David Korn said. He noted that the magazine has a medical advisory board, and suggested that a strong letter should be sent to that board and to the publisher. . . . **AMERICAN CANCER** Society and a coalition of cancer researchers and environmental groups have petitioned the Dept. of the Interior to declare the Pacific Yew tree, the only source of the drug taxol, a "threatened species." The drug is showing positive results in treating ovarian cancer. . . . **COORDINATING COUNCIL** for Cancer Research, a nonprofit organization formed to support worldwide collaboration among teams of research scientists, has changed its name. It will now be known as the International Coordinating Council for Cancer Research. The change was made to underline the group's international emphasis. ICCR is headed by Jacques Crozemarie, chairman and founder, and Vincent DeVita, president. . . . **AWARDS, HONORS** to NCI staff: PHS Outstanding Service Medals to **Charles "Snuffy" Myers, Ilan Kirsch, Jerry Rice** and **James Mulshine.** Special Recognition Award to **Louise Brinton.** Distinguished Service Medal to **Robert Hoover.** Meritorious Service Medals to **Mitchell Gail** and **Margaret Tucker.** NIH Director's Awards to **Jeffrey Norton, Paulette Gray, William Blattner.** AACR/Upjohn Young Investigator Award to **Richard Alexander.** ASCO/Upjohn Award to **Douglas Schwartzentruber.** Southern Thoracic Society President's Award to **Harvey Pass.** NIH Merit Award to **Rosemary Cuddy.** American Assn. for Clinical Chemistry honored **Robert Gallo,** chief of the Laboratory of Tumor Cell Biology. **Neal Copeland,** head of the Mammalian Genetics Laboratory at the Frederick Cancer Research Facility, received the Elliott Osserman Award of the Israel Cancer Research Fund.

Senate Bill Provides 7% Increase; Mandates Dietary Intervention Trial

(Continued from page 1)

which was $1.749 billion, not including about $40 million for training. The Senate amount included the $40 million. The House figure would have provided about a $150 million increase above FY 1990, while the Senate amount provides a $113 million increase. Both figures include AIDS funding.

The only explanation for the Senate's much lower amount seems to be the Iraqi invasion of Kuwait, which took place after the House appropriation.

The bill, submitted by the Senate Labor, HHS, Education Subcommittee, survived a last-minute attempt by some senators on the full appropriations committee to take an across the board cut from health and education programs to put toward AIDS treatment under the AIDS-care law signed by President Bush in August.

The bill provides NIH a total of $8.347 billion, a $419 million above the Administration's request and $770.7 million over the FY 1990 appropriation. The committee said that amount would restore the number of new grants to 6,000.

At NCI, the percentage of approved grants that could be funded under the Senate figure is approximately 27 or 28 percent. More detailed budget estimates for NCI programs by mechanism are expected to be available later this week.

Like the House, the Senate committee said NCI should place more emphasis on cancer prevention and control. However, the Senate was more specific and included $25 million for "significant expansion" of prevention and control research. In a major victory for advocates of dietary intervention, the committee said $5 million of that amount is to go toward a dietary cancer and heart disease prevention trial. The Senate directed NCI to "make every effort to initiate" such a trial.

The committee also:

▸urged NCI to establish two additional cancer centers in rural areas and added $2 million for this purpose. The committee said it included "adequate funding" to maintain existing cancer centers.

▸urged NCI to expand information dissemination activities and included $5 million for the effort.

▸directed NCI to increase funding for clinical trials.

▸provided NCI with the ability to move up to $5 million toward facilities construction.

▸added $3 million for retroviral research.

▸added $4 million for pediatric AIDS research.

Senate Revives Dietary Trial

The Senate committee said it was "disturbed" that NCI's prevention and control budget of $75 million is less than 5 percent of the Institute's budget.

"Current information indicates that specific emphasis should be placed on research initiatives in such areas as factors affecting the incidence of cancer in minority populations, dietary intervention trials and alterations in lifestyle to decrease cancer risk," the Senate committee said in its budget report. "For example, it has been estimated that specific dietary changes may be able to reduce total cancer mortality rates by about 35 percent."

The committee directed NCI, in collaboration with the National Heart, Lung & Blood Institute, to "make every effort to initiate" a dietary cancer and heart disease prevention trial.

"This study should evaluate whether or not a simple dietary change that emphasizes total fat reduction will prevent the occurrence of prominent cancers and coronary heart disease among postmenopausal women. Such women are currently experiencing an epidemic of breast cancer, and experience heart disease at about the same rate as men, but with a higher case fatality rate. Available data suggest that a 50 percent reduction in dietary fat may lead to reductions by 50 percent or more in the rates of occurrence of cancers of the breast, colon, ovary and uterus, and reductions by 30 percent or more in coronary heart disease in postmenopausal women."

The committee was undoubtedly referring to the effort last year by principal investigators Maureen Henderson and Ross Prentice of Fred Hutchinson Cancer Research Center in Seattle, who submitted an RO1 for a Dietary Fat Intervention Trial in Women to NCI and NHLBI. Despite a positive scientific review of the trial, the National Cancer Advisory Board voted

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against funding the trial because of unanswered scientific questions and because of the trial's cost, an estimated $12 million a year (**The Cancer Letter,** Dec. 8, 1989).

Div. of Cancer Prevention & Control Director Peter Greenwald had supported the trial, and in NCI's FY 1992 bypass budget, the trial was mentioned as one that could be funded if NCI were to receive the bypass amount.

The DCPC Board of Scientific Counselors, which also expressed its support for such a trial, is scheduled to consider a concept for a dietary intervention trial at its meeting this week.

"The scientific methodology exists to proceed with such a study, and the committee directs NCI and NHLBI to cooperatively and aggressively move forward on an intervention trial," the Senate report said. "The committee directs that within 90 days, the Institutes must submit a report to Congress detailing, among other things, proposed scope of plan, budget, mechanisms for jointly implementing this study and its starting date. The committee has provided up to $5 million of additional funding for this effort."

The committee also directed NCI to submit within six months a spending plan "outlining the specific initiatives, including those recommended by the committee, it intends to undertake in the crucial area of cancer prevention and control."

NCI directors have generally heeded the wishes of the Congressional appropriations committees when the same language appears in House and Senate reports. The House committee was less specific, but did mention that dietary changes are believed to have the effect of reducing mortality rates of some cancers.

'War On Cancer' Praised

Despite its lower budget recommendation, the Senate committee was generally more supportive of NCI in tone than the House, which said in its report that "the American people expect more from their $1.8 billion annual support of the National Cancer Program" (**The Cancer Letter,** July 20).

The Senate seemed to wish it could provide more. "It is clear that the proper resources to continue to drive the exciting and productive research in cancer must be enhanced," the committee said.

In its report, the Senate committee said it was "pleased" that there has been a measurable decline in the mortality rates for a number of common cancers. "The advances in medical research and many of the tremendous breakthroughs we are seeing today are a direct result of the war on cancer begun in 1971. The mortality rate for cancer in persons under the age of 65 has improved dramatically in a number of areas. As an example, the death rate from Hodgkins disease has decreased by 52 percent, from testicular cancer by 61 percent, from ovarian cancer by 25 percent and from cervical cancer by 35 percent."

In contrast, the House said it found mortality rates "discouraging."

However, the Senate said a "major concern" is the continuing increase in the overall cancer incidence rate. The Senate also noted that "certain categories of individuals have not benefited equally" from advances in detection, prevention and treatment.

"Minority groups, the poor, the medically underserved particularly those in rural America, and those over age 65 continue to experience disproportionately high cancer mortality rates," the Senate report said. "The reasons for these disparities are complex, and may relate in part to the lack of ready access to state of the art prevention, early detection and treatment methodology by these population groups."

The Senate directed NCI to "continue to strengthen its outreach efforts so that the benefits derived from the major advances in cancer prevention and treatment made since the inception of the National Cancer Program can be extended equally, with all Americans sharing in the fruits of this progress."

Other areas the Senate highlighted:

Rural health--The Senate continued to emphasize rural health. The subcommittee chairman, Sen. Tom Harkin, is a Democrat from Iowa.

"The committee continues to be concerned with the issue of increased cancer incidence that is experienced by rural population groups and its pleased that NCI has taken steps to establish a task force to evaluate the special problems associated with the prevention, early detection and treatment of cancer in the rural setting. In addition, an expansion of the NCI's SEER program to include additional statistical data bases in rural areas is currently underway."

Health and behavior--The Senate committee noted the Surgeon General's 1989 report on smoking, which stated that only 10 percent of smokers start the habit after age 21.

"To achieve our year 2000 health objectives goal of reducing cancer rates by 50 percent, it is essential that a major causal factor of cancer--smoking--be dramatically diminished," the committee said. "Special attention should be placed on those under the age of 21, as evidence clearly demonstrates that smoking begins primarily during childhood and adolescence. The committee, therefore, directs NCI to invest more heavily in behavioral research as it relates to preventing risk behaviors associated with cancer, with

special emphasis on averting youth and minorities from smoking."

The committee said it included funding to continue the Community Intervention Trial for Smoking Cessation (COMMIT) and the American Stop Smoking Intervention Study (ASSIST). Funding was also included for NCI to continue a breast cancer screening awareness program to promote mammography, in conjunction with the Centers for Disease Control. "A cooperative network of intervention studies in seven states is currently in place to improve the utilization of mammography, breast exams and breast self-examination. The committee urges NCI to continue its collaboration with the CDC to identify the barriers which discourage women from being screened for cervical cancer by obtaining pap smears on a regular basis," the Senate said.

Information dissemination--The committee urged NCI to expand information dissemination activities, and said it views these activities as "an integral part of the Institute's efforts to achieve its overall goal of reducing cancer mortality nationwide." It added $5 million for this effort.

The committee said NCI should encourage physicians to avail themselves of computer technology to access the Physician's Data Query system, which provides information on treatment protocols. The committee also noted that the Cancer Information Service answered 500,000 phone queries last year.

Cancer centers--The committee commended NCI for "revising its criteria for the comprehensive cancer centers designation to include within these criteria a need for the center to provide outreach activities within the surrounding community. Comprehensive cancer centers must first define their communities by maintaining productive outreach efforts to identify local cancer issues and problems and then carry out appropriate cancer prevention and control activities to meet these needs. In this fashion, comprehensive cancer centers act to specifically address the issues which affect the populations within their communities who experience disproportionately high cancer incidence and mortality rates. The committee considers this to be a major component and justification for the support of comprehensive cancer centers."

The committee encouraged NCI to "continue to explore innovative ways of enhancing the geographic diversity of centers" and said it was concerned that "large areas of the rural Midwest" are not served by a comprehensive cancer center "in spite of the high incidence of cancers in this area due to the high exposure to agricultural chemicals."

"The committee urges the establishment of two additional cancer centers to serve underserved rural areas and recommends that the Univ. of Iowa be carefully considered for such a center, and has added up to $2 million for the purpose of new centers. Additionally, adequate funding is available to maintain existing centers with appropriate inflationary adjustments."

NCI did not have available its breakdown of its budget estimates by mechanism by **The Cancer Letter's** presstime this week, so it is not clear how much centers will actually receive under the Senate bill.

The committee encouraged centers to include "high quality counseling services" to cancer patients, and expects NCI to provide a report on this effort by next February.

Cancer vaccines--The committee said that it included funding for development of a cancer vaccine. The report noted that, "A grant was recently awarded to conduct a phase 3 clinical trial to evaluate the use of a vaccine as an adjuvant or postsurgical therapy for preventing recurrence of stage 3 melanoma. The committee also strongly supports continued work in cancer biology and adaptive cellular therapy. The committee said it was "pleased" that NCI has scheduled a conference on vaccines (to be held Oct. 29-30 at NIH).

Emergency priorities--The committee appeared to give NCI a mandate to pursue high-priority research. "The area of cancer research, and biomedical science itself is moving at an unprecedented rate," the committee said, citing the recent NCI collaboration with NHLBI on gene transfer therapy. "The Institute should continue to move quickly to pursue new research leads and should utilize whichever funding mechanism is the most appropriate to best capitalize on these promising opportunities."

Clinical trials--The committee said it recognized the importance of clinical trials in reaching conclusions about treatment options. "The committee is becoming increasingly concerned with funding levels for cancer clinical research. It is very important that randomized clinical trials, such as those which have proven the efficacy of chemotherapy in colon and breast cancer, and of the growth factors in decreasing toxicity, be funded appropriately so that basic research advances can be brought to bear on cancer patient care. The committee, therefore, directs that NCI increase clinical trial funding beyond the 2.5 percent increase proposed by the Administration."

Until NCI releases its budget estimates, it is not clear how much of an increase this will mean. One NCI source, however, noted that treatment clinical trials probably will get a small increase, while

prevention trials will see a major increase.

Facilities--The committee said the need to upgrade and modernize extramural biomedical facilities, including cancer centers, is "of great concern." Up to $5 million, within available funds, could be used to make construction awards, and first priority should go to projects that were approved but unfunded prior to 1990, the committee said.

(Editor's note: The amount the Senate included for construction is predicated on NCI's construction authority, which is granted under a separate NIH authorization. NIH's authority ran out Oct. 1 and House and Senate versions of the reauthorization measures are still pending. Two congressmen, Sen. William Armstrong (R-CO) and Sen. Gordon Humphrey (R-NH), have put "holds" on the Senate bill having to do with fetal tissue research and the Biomedical Ethics Board.)

Retrovirus research--The committee said it was "encouraged" by NCI's new program in retrovirus research, and provided $3 million for continuation of this effort.

Native Americans--The committee said it approved of NCI's effort at initial definition of the cancer control needs of native Americans, for which $9 million was targeted last year. The committee urged NCI to increase its commitment and said the following areas should be targeted: "Cancer intervention research to identify population specific and culturally appropriate interventions which will reduce the burden of cancer in these populations; cancer prevention and control research training programs for American Indians, Alaska natives, native Hawaiians and American Samoans." The committee said it was especially concerned about cancer incidence among American Samoans and asked NCI to develop a five year plan for addressing their needs.

AIDS--The committee said it provided up to $4 million for pediatric AIDS research.

International research--The committee requested a report from NCI in conjunction with the Fogarty International Center, on "cancer research priorities which should be pursued on an international basis and particularly what NCI can and will be doing to focus and provide increased support for these programs."

AIDS Funding Tops $2 Billion

The Senate provided nearly $2.185 billion for Public Health Service spending on AIDS, about $562 million more than the Administration request and $518 million more than the House provision. Not included in the bill, but also within PHS, is $63.2 million for AIDS activities of the FDA and $1.013 million for AIDS activities of the Indian Health Service.

The committee said it provided a total increase of $10 million for an expansion of basic research in pediatric AIDS.

In its discussion of NIH, the Senate committee said it concurred with the House that NIH needs to implement long range planning and improved fiscal management related to the number of new grants approved each year and the high level of across the board cuts ("downward negotiations") in grant awards (**The Cancer Letter**, July 20).

The committee said it believed the problem was the result of the lengthening average time of awards, and the 94 percent increase since 1981 of the average cost of awards.

"An additional trend which causes false expectations in the research community is the upward creep in the NIH approval rate of grant applications. Since 1972 the percentage of grants approved has increased from 69 percent to the 1991 estimate of 95.3 percent. Clearly this trend increases expectations for funding and also results in an ever declining award rate of grants."

The committee agreed with the House that an NIH plan should include a cost control system to ensure that the average length of grants does not exceed 4 years and that the average cost not increase faster than the biomedical research inflation index. In addition, the total cost of a grant should be considered at all stages of the review process and study sections should consider whether a project merits funding. The Senate did not say that downward negotiations should not take place this year, an item in the House report that worried NCI officials.

The Senate committee, unlike the House, did not mention limiting the number of centers for NIH as a whole. That House recommendation caused worry at NCI at the extramural community that cancer centers would be lumped in with other NIH-supported centers in some overall limit.

NIH Director's Term

The Senate also said the appointment of an NIH director should not be subject to political considerations. The director should be appointed for a five-year term overlapping Presidential terms, and the committee included language in the bill to make the change in law. The committee also provided the NIH director the ability to transfer up to 1 percent of any account to high priority research opportunities.

The committee also provided the NIH Office of the Director with $15 million for extramural construction. The committee also said it supports continued funding of the Jackson Laboratory and Univ. of Kansas.

Working Group Initiates Preclinical Studies Of AIDS-Related Lymphoma

An informal NCI AIDS Lymphoma Working Group has been established to coordinate preclinical research leading to the development of new methods for treatment and prevention of AIDS associated non)Hodgkin's lymphoma.

Judy Karp, special assistant to NCI Director Samuel Broder, chairs the group which includes eight to 10 members from the Div. of Cancer Biology, Diagnosis, & Centers; Div. of Cancer Etiology; and Div. of Cancer Treatment.

Karp briefed the National Cancer Advisory Board earlier this month on the purpose and activities of the group.

Purpose:

1. To define cellular, humoral, and/or viral mechanisms of B cell activation and eventual malignant transformation in AIDS.

2. To identify means of abrogating unrestrained B cell proliferation before irreversible clonal expansion ensues.

3. Ultimately, to translate the preclinical findings into clinical trials aimed at both treatment and prevention.

Selected targets for preclinical investigation:

1. Genesis, perpetuation and expansion of clonal B cell activation.

A. Role of B stimulatory lymphokines--initial focus on IL-6; other targets include IL-4, IL-10, 12KD b cell growth factor.

B. Role of monocyte/macrophage--reservoir for virus; factory for lymphokine production.

2. Identification of lymphokine inhibitors, lymphocytic (antilymphoma) drugs, and antiviral compounds; use of drug screening, with focus on natural products.

3. Establishment of new lymphoma cell lines from AIDS related lymphomas for the purpose of:

A. Biochemical characterization--unique surface determinants (at unusual sites, CNS, GI); reactivity against HIV and/or other viral antigens; constitutive lymphokine production.

B. Target cells for drug and lymphokine inhibitor assays.

4. Prediction of high risk for "lymphoma genesis" by longitudinal monitoring of serum and CSF from initial detection of HIV for:

--Presence and magnitude of lymphokines.

--Immunoglobulin levels.

--Presence and magnitude of viral antigens and antibodies.

Those investigations will be carried out in appropriate laboratories of the three divisions.

Karp noted that DCE and DCT have each issued an RFA in this area. The DCE RFA is for research on mechanisms of viral induced AIDS associated neoplasia; the DCT RFA is for development of an AIDS lymphoma network.

Robert Yarchoan, senior clinical investigator in the Div. of Cancer Treatment's Clinical Oncology Program, told the NCAB that the actual number of AIDS related lymphomas in the next five years may be higher than previously thought. The increasing incidence in men age 21 to 49 is almost entirely due to the AIDS epidemic, he said.

Noting the concern by some that AZT, so far the only drug approved for treatment of AIDS, may cause some lymphoma, Yarchoan said that is "unlikely. Many AIDS patients who have never received AZT get lymphoma. These patients are already severely immunosuppressed."

AZT does not cause cancer in most animal tests, although lifelong studies of rodents receiving high dose AZT can cause some malignant tumors, "so a direct role of AZT can't be ruled out."

Yarchoan suggested as possible directions for future research:

1. Improve understanding of the pathogenesis of AIDS related lymphoma.

2. Explore means of preventing lymphoma.

3. Determine if early therapy of HIV infection can prevent or delay lymphoma.

Update Of 1976 Fluoride Study Finds No Evidence Of Increased Risk

A recent report from the National Toxicology Program that fluoride was carcinogenic in an animal study caused NCI to review and update a 1976 epidemiology study, the largest of at least 50 different studies looking at the health risk of fluoridated drinking water.

The conclusion in 1976 was that there was no pattern of increased risk of cancer. Robert Hoover, chief of the Environmental Epidemiology Branch in the Div. of Cancer Etiology, told the National Cancer Advisory Board that the new review did not change that conclusion.

DCE Director Richard Adamson said that the NTP study involved administration of fluoride at three dose levels--25, 100, and 175 parts per million--in the drinking water of mice and rats. There was no evidence of carcinogenicity in female rodents at any dose level. At the highest dose, osteosarcoma was

seen in one of 50 mice and three of 85 rats. There was one cancer in a control group of female mice.

Hoover noted that over 40 years, the addition of fluoride to drinking water to prevent dental caries had been controversial, prompting the various studies. The 1976 study involved mortality data from 1950 to 1969. "All reached the same conclusion: no evidence of increased risk."

The epidemiology study looked especially for bone cancer, the apparent most likely malignancy that might be related to fluoride. They also looked at all cancer sites. "There were no trends associated with the consumption of fluoridated drinking water," Hoover said.

"We had thought this issue had been laid to rest years ago," NCI Director Samuel Broder said. "But a sister agency presented pathological data, and we felt we needed to respond. We knew we could do it quickly, and get a reasonably definitive answer. It was an emergency, crash program. We promised Congress we would get a rapid answer. We're not planning to do another fluoride study."

NCAB member John Durant objected to the "outlandish doses that are not relevant to humans." The fluoride added to drinking water amounts to one part per million, although Hoover acknowledged that there is frequently other exposure to fluoride, such as in toothpaste and some foods.

Extremely high doses may in themselves cause cancer without regard to the carcinogenic nature of the substance tested, Durant said, referring to a recent report by Univ. of California (Berkeley) scientist Bruce Ames. "When are we going to do toxicity studies at relevant doses?"

Adamson said that NTP uses the maximum tolerated dose as the high dose in bioassays, and then goes down from that for different dose levels.

Miriam Davis, who represents the National Institute of Environmental Health Sciences, the parent agency of NTP, on the NCAB, observed that amounts of fluoride concentrated in bones of humans who drink fluoridated water is not significantly different from that in the bones of the animals in the studies.

NCAB member Howard Temin said "there is a rationale for high doses. It is so we do not have to test several million rats. It is not unreasonable."

NCI High School Summer Program Called "Astonishingly Successful"

A Summer Enrichment Program designed to stimulate interest of high school students in careers as scientists was carried out last summer by NCI at Hood College, in Frederick, MD. "It was an astonishingly good start," Director Samuel Broder said.

Claudia Baquet, associate director of the Cancer Control Science Program of the Div. of Cancer Prevention & Control, reported on the program to the National Cancer Advisory Board.

One hundred seven rising 10th graders, from 25 states, spent six weeks, living and studying at Hood College. Faculty and NCI staff carrying out the program also lived there. Students attended classes from 8 a.m. to 3 p.m. four days a week. On the fifth day, they went on field trips, which included NIH and Frederick Cancer Research Center laboratories, the Smithsonian museums, and Harpers Ferry, among others.

"How much did it cost and how can we have one at Wisconsin?" NCAB member Howard Temin asked. He flinched when Baquet said the total cost was $500,000, but DCPC Director Peter Greenwald pointed out that that was for a national program, involving travel from 25 states. It would be considerably less for a state or local program.

NCAB Chairman David Korn said that Stanford has a similar program, with a budget of $700,000. "It's terribly important to do, but it has to be done well."

Broder said the program "may well have failed were it not for the astonishing enthusiasm of our staff. It is an experiment, and is within our jurisdiction, for training. We would like to see it replicated, and will be delighted to help."

The program will be evaluated, and success will be measured by the number of students who select careers in science, by their selection of colleges and universities, and by their grades in science courses, Baquet said.

RFAs Available

RFA CA-91-02

Title: Epidemiology of cancer in U.S. ethnic/minority populations
Application Receipt Date: February 15, 1991

The Div. of Cancer Etiology of NCI invites grant applications for epidemiologic studies of possible causes of cancer in U.S. ethnic/minority populations.

The purpose of this RFA is to stimulate analytical, site-specific studies of cancer etiology in ethnic/minority populations of the U.S. Research strategies may involve cohort, case-control, or genetic epidemiology designs as well as laboratory methodology. Innovative approaches that involve new inter-disciplinary collaboration, or include the application of diagnostic or exposure measurements, are particularly encouraged. Whenever possible, studies should make cost-efficient use of existing resources such as population-based cancer registries or specimen repositories. Emphasis should be placed on etiologic studies of the more common cancers affecting the U.S. population, or on cancer sites with rising incidence rates. Projects will be evaluated on their potential for impact on the overall understanding of cancer

etiology and means of prevention.

The initiative permits a wide range of epidemiologic investigations of cancer in U.S. ethnic/minority populations including, but not limited to, the following:

--Cross-cultural studies of cancers with striking ethnic disparities in incidence rates, among groups residing in the same or different geographic areas, to identify more specifically the etiologic factors, and to study their relationship with biomarkers of exposure.

--Analytic studies of specific cancer sites to determine the impact of age-specific changes in exposure over time, due to waves of migration within the U.S. as well as from other countries, and/or to secular changes in lifestyle, occupation, and environment.

--Studies among Hispanics with special consideration given to the subgroups within the population.

--Studies of ethnic differences in the histologic and cytologic parameters of particular cancers that may reflect differences in exposures or susceptibility.

--Meta-analysis of previous studies to further refine known associations or yield new information on risk factors.

--Studies addressing methodological issues related to the heterogeneity of ethnic groups, especially dietary and genetic parameters.

--Molecular epidemiologic studies exploring differences in genetic predisposition to cancer due to variations in carcinogen metabolism, DNA repair activities, response to tumor promoters, measures of immune function, chromosome sensitivity to mutagens, or other factors.

--Genetic epidemiologic studies of polymorphisms associated with ethnic differences in cancer risk.

In any studies involving human subjects, where feasible and appropriate, women should be included in the study population; otherwise a clear rationale for their exclusion must be provided in the application. Minority institutions are encouraged to apply, and other institutions are encouraged to establish collaborative arrangements with minority institutions.

Copies of the RFA may be obtained from Dr. A.R. Patel, Extramural Programs Branch, Epidemiology and Biostatistics Program, Div. of Cancer Etiology, NCI, Executive Plaza North, Suite 535, Rockville, MD 20892, phone 301/496-9600.

RFA CA-91-01

Title: AIDS-lymphoma network

Letter of Intent Receipt Date: December 16

Application Receipt Date: January 16, 1991

NCI's Div. of Cancer Treatment invites applications from interested investigators to participate in an AIDS-Lymphoma Network. The AIDS-Lymphoma Network will be composed of those institutions who successfully compete for funding in this RFA to perform new therapeutic AIDS-Lymphoma clinical trials, or AIDS-Lymphoma clinical trials with correlative laboratory studies. The purpose of the AIDS-Lymphoma Network is to foster interchange among different institutions and to coordinate activities of the different institutions working towards a common goal.

Adult and pediatric AIDS patients are surviving longer due to improved retroviral and opportunistic infection treatment and care. As a result, acquired immunodeficiency syndrome-associated malignancies have become more prevalent and are now a major concern. Lymphomas and Kaposi sarcomas are the malignancies most frequently seen in AIDS patients. Both non-Hodgkin's lymphoma and Hodgkin's disease have been described in these patients. The etiology of NHL in AIDS patients remains unclear. The most prominent clinical features of NHL in HIV-positive patients are the aggressive nature and course of the disease and the presence of unusual extralymphatic disease in sites such as the CNS or bowel.

Results of treatment using standard intensive multi-agent chemotherapy have been disappointing, with median survival of less than one year in treated patients, and difficult because conventional aggressive combination chemotherapy exacerbates the patient's immunodeficient state. The choice of therapy must be based on the nature of the disease and the overall condition of the patient. The precise relationship of HD to the underlying immunodeficient state in patients with HIV infection also remains unclear. Clinical observations suggest that HD in this setting may have a different natural history and therapeutic outcome when compared with HD in the general population. Patients with HIV infection and HD are likely to have a poor therapeutic outcome and to develop AIDS-associated opportunistic infections during therapy.

NCI recognizes that research in AIDS-lymphoma is technically difficult to conduct because of the complexity of this disease and the relatively limited availability of study subjects at any single institution. Thus it is encouraging conduct of research relevant to this RFA in the context of an AIDS-Lymphoma Network. The AIDS-Lymphoma Network will serve as a resource of information and will work to facilitate patient accrual, obtaining tissue samples, and exchange of information and materials between involved investigators.

The major goal of this RFA is to develop more effective management and therapies for AIDS-lymphoma. This goal can be accomplished by supporting (1) the development of AIDS-lymphoma therapeutic clinical trials or (2) AIDS-lymphoma clinical trials with correlative laboratory studies.

Both adult and pediatric AIDS-lymphoma studies involving non-Hodgkin's and Hodgkin's disease are encouraged. The therapeutic clinical trials (pilot, phase 1, or phase 2) will usually involve a patient population ranging between 5-40 patients with survival, response, and/or quality of life end points. NCI does not envision the establishment of multi-institutional collaborative therapeutic clinical trials by the AIDS-Lymphoma Network at this time.

Some examples of potential correlative laboratory studies could deal with the following: (1) What is the clinical significance of the abnormal patterns of distribution of disease sites? (2) What factors are involved in the different clinical responses observed in AIDS-lymphomas? (3) What are the potentially exploitable features with respect to etiology and pathogenesis of AIDS-lymphoma? (4) What is the clinical significance of the molecular and cytogenetic alterations specifically associated with AIDS-lymphoma? (5) What alterations occur in growth factors or oncogenes in AIDS-lymphoma patients that may potentially lead to new therapies? Investigators are not limited to the above categories of potential studies. Other scientific approaches may be proposed.

Approximately $3 million in total costs per year for three years will be committed to fund applications. It is anticipated that 10 to 15 awards will be made. The earliest feasible start date for the initial award will be July 16, 1991. Although this program is provided for in the financial plans of the NCI, the award of grants pursuant to this RFA is contingent upon the availability of funds appropriated for fiscal year 1991.

Applicant organizations should be located in the United States and Canada. Non-profit and for-profit organizations and institutions, and government agencies are eligible to apply.

For a copy of the complete RFA describing research goals and scope, contact Dr. Roy S. Wu, Health Scientist Administrator, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North, Room 734, Bethesda, MD 20892, phone 301/496-8866, FAX 301/496-9384.