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Four NCAB Appointments Announced, Including Durant, Fisher; White House Delays On Others

President Reagan has filled four of the six vacant positions on the National Cancer Advisory Board, including the appointment of two nationally prominent clinician scientists with indisputable credentials--John Durant and Bernard Fisher.

(Continued to page 2)

In Brief

More Than 1,600 Taking First Oncology Nurse Certification Exam; FCC Discussions Planned

TOTAL NUMBER of nurses signed up to take the first oncology nursing certification examination April 30 in Los Angeles is 1,642. Oncology nursing certification is being sponsored by the Oncology Nursing Society, which will start its 11th annual Congress that day.... **FREESTANDING CANCER** center development conference in Philadelphia May 13-14 will include discussion of clinical issues such as the role of surgeons in freestanding cancer centers; hospital relationships; economic issues including joint ventures and marketing; community relations; and national networking. The conference is sponsored by Fox Chase Cancer Center (and will be held there), Intercommunity Cancer Centers of America and CDP Associates. . . . **MAY 24-JUNE 1** has been designated by Congress ans "Older Americans/Skin Cancer Prevention and Detection Week." The American Academy of Dermatology will sponsor free education and screening programs throughout the country that week. . . . **RICCARDO DALLA-FAVERA**, whose research first demonstrated the presence of a genetic alteration in the cells of patients with acute leukemia, will be awarded the Leukemia Society of America's first President's Research Development Award, a $50,000 grant. Dalla-Favera is assistant professor of pathology at New York Univ. School of Medicine.... **LEUKEMIA SOCIETY** of American estimates there will be 70,100 new cases of leukemia, lymphoma and multiple myeloma in the U.S. this year. Of that number, 26,000 will be leukemia, about have acute and half chronic. Overall survival rate for leukemia has doubled in the last 20 years, from 15% to 33% in 1986, according to Lawrence Ellis, the Society's national president. . . . **ZANVIL COHN**, head of the laboratory of cellular physiology and immunology at Rockefeller Univ., has been named the university's first Henry G. Kunkel professor.

ACS Asks Congress For $1.32 Billion NCI '87 Budget
. . . Page 3

Phase 1 Study Asked To Determine If Drug Administration Timing Improves Results
. . . Page 4

Diet Intervention Results Could Be Found In Months
. . . Page 4

New Tool Found To Cut DNA At Any Position
. . . Page 7

Program Announcement
. . . Page 8

Fisher, Durant, Two Others Named To NCAB; Korn Reappointed Chair

(Continued from page 1)

The other two appointments announced last week were to fill the two lay member vacancies. They went to Nancy Goodman Brinker of Dallas and Phillip Frost of Miami.

The President also announced that David Korn was appointed to another two year term as chairman of the Board. That term, as chairman, will expire in March, 1988, although Korn will still have two years left on his term as a member of the Board. Korn is vice president and dean of Stanford Univ. Medical school. He is 53.

Durant, President of Fox Chase Cancer Center, was named to replace William Powers, chief of radiation oncology at Wayne State Univ. who completed two six year terms on the Board. Durant is the current president of the American Society of Clinical Oncology and was the first director of the Univ. of Alabama Comprehensive Cancer Center before assuming his present position at Fox Chase. He is also adjunct professor of medicine at the Univ. of Pennsylvania School of Medicine. He is 55.

Fisher, professor of surgery at the Univ. of Pittsburgh and director of oncology at the School of Medicine there, replaces another surgeon, LaSalle Leffall, chairman of surgery at Howard Univ. Leffall completed one term on the Board. Fisher, 67, is chairman of the National Surgical Advjuvant Breast & Bowel Project, one of the major cooperative groups whose clinical studies have had a significant impact on the management of breast cancer. He also served a term as a member of the President's Cancer Panel.

Brinker succeeds Eppie Lederer (Ann Landers) as one of the Board's six lay members. A breast cancer patient herself, she is founder and chairman of the Susan G. Komen Foundation, established to aid the advancement of cancer research and named in honor of her sister, who died of breast cancer. She is an organizer, with Rose Kushner, of the National Alliance of Breast Cancer Organizations, which includes more than 1,000 support groups around the country. Brinker is 39.

Frost, 49, takes over the seat held by Kushner. He is chairman of Key Pharmaceuticals of Miami and is an MD (Albert Einstein, 1961).

The White House offered no explanation for the delay in announcing the other two appointments. Those are the seats held by Robert Hickey, executive vice president of the Univ. of Texas System Cancer Center/M.D. Anderson Hospital, and Gale Katterhagen, who this week became director of the Comprehensive Cancer System at Memorial Medical Center in Springfield, IL.

All of the retiring members of the Board were appointed by President Jimmy Carter. It has been anticipated that, as a matter of policy, President Reagan would not retain any Carter appointees on the Board. However, the Assn. of Community Cancer Centers has mounted an intensive campaign for Katterhagen and for John Yarbro, Univ. of Missouri professor of oncology. Both are former ACCC presidents.

There was speculation that Reagan's advisors recommended holding the two seats open until they could reach a decision on whether to go along with ACCC on one or both of its suggestions. The Oncology Nursing Society also developed an intensive campaign for the appointment of one or both of two of its members, Marilyn Stromberg of Illinois and Joyce Yasko of Pittsburgh.

Apparently, two of the needs NCI Director Vincent DeVita felt were most pressing have been filled. With both Leffall and Hickey leaving, DeVita thought it imperative that at least one of the new members be a strong, creditable, academic surgical oncologist. Fisher certainly is all of that, although he has been at odds at times with some of his surgery colleagues in the breast cancer field.

DeVita also felt the Board should have at least one member who is a strong research oriented academic medical oncologist, and Durant fits that description, perhaps as well as anyone could.

Still another deficiency which has existed on the Board since Maureen Henderson's term expired is the lack of an expert in the public health-epidemiology-cancer control field.

Obviously, the President cannot satisfy both ACCC and ONS while also appointing an epidemiologist-cancer control specialist.

Hickey, Leffall and Powers were among the Board's strongest members. Although each contributed significantly in their respective fields, their impact and advice transcended their own specialties. Powers and Hickey fought successfully for retention and expansion of the Organ Systems Program, and Leffall led development of programs addressing problems of cancer in blacks.

ACS Asks Congress For NCI Budget Of $1.32 Billion In 1987 Fiscal Year

The American Cancer Society's Board of Directors has approved a resolution calling on Congress to appropriate $1.32 billion for NCI for the 1987 fiscal year. The Board also passed resolutions asking for bans on all cigarette and smokeless tobacco advertising and for passage of the High Risk Disease Notification and Prevention Act.

ACS President Charles LeMaistre is scheduled to appear before the House HHS Appropriations Subcommittee April 24 to make the case for an NCI budget of $1.32 billion.

An ACS position statement on the budget acknowledges that "FY 1987 poses a fiscal problem more severe than any previously faced by the government." It specifically cites Congress' attempt to control the deficit with the Gramm-Rudman-Hollings Act.

"With rare exception, no government program will be spared the effects" of GRH, the statement notes. NCI "is scheduled to lose $64 million the first year, and $60 million the second. If the projected scenario is played out as currently expected, the NCI budget would be reduced from $1.258 billion which it was supposed to get in FY '86 to $1.194 billion in FY '87. This would result in numerous significant cuts in NCI's program, including loss of federal funding for five comprehensive cancer centers, major reductions in the Organ Systems Program, marginal funding for the remaining centers, loss of some vital clinical cooperative groups, and severe cuts in the cancer communications program, among others. Research grants would be reduced 10 to 20% across the board."

ACS asserts that "severe loss of the momentum in progress against cancer through research, prevention and treatment that is so vital to a dynamic program would result.

"It is the position of the Society that cancer does not recognize or acknowledge the problems that government has with its finances. Cancer knows no boundaries, is apolitical, and will continue cutting its inexorable swath through the lives and means of Americans, regardless of Medicare cuts, defense appropriations or GRH."

ACS also asserts that "neither do the American people have much tolerance for the effects of an up and down economy on the battle against cancer. With them, cancer is the top health priority. Every year the American people renew their expression of this priority through significant increases in their support of the (ACS) programs of research, support, education and service. The Society carries out its programs with no funds of any kind from government, and because of this, is in a unique position among private sector organizations to speak with independence and objectivity on national cancer research and treatment support needs.

"It is the position of ACS that while we agree in principle with the objectives of Gramm-Rudman-Hollings, we do not believe that the (NCI) budget should be cut.

The statement said that the "small proposed increase" it is seeking "would serve to maintain the level of momentum vital to assuring continued progress against this disease.

"The dynamics of progress against cancer cannot survive abrupt reductions, program cancelations, and the kind of across the board disruptions in personnel and other forms of encouragement and support that solid, reliable program continuation represents. Cancer has no respect for man's other problems, and continues to drain the energies and resources of our nation and its people to the tune of approximately $40 billion a year in lost wages, jobs, medical costs and other factors."

The statement continues, "Responsible members of society, individuals and organizations like ACS must act responsibly and do our part in sharing the solutions as well as the cause of our contemporary fiscal problem. That is why ACS believes that a minimal increase in NCI appropriations would carry the National Cancer Program through this crucial period in our nation's economic history."

The antitobacco advertising resolution proposes that as a first step, all models and scenery in tobacco advertising be eliminated, with illustrations limited to the depictions of cigarette packages (in the case of cigarette ads). It recommends that advertising copy merely feature the tar and nicotine content of the product, one of the four rotating warning messages from the Surgeon General, and the price of the product. The resolution also calls for a complete end to cigarette company sponsorship of sports and other events that attract young people.

The third resolution supports the intent of S 2050 and HR 1309, the high risk notification legislation.

Chronobiological Staging of Drug Administration Phase 1 Study Asked

Phase 1 trials of chronotherapy should be considered to determine whether the effectiveness of chemotherapy can be enhanced by chronobiological staging of drugs in cancer patients, Robert Klevecz told the American Cancer Society's annual Science Writers Seminar last week in Daytona Beach.

Klevecz asserted that "there is good evidence " the dose of a chemotherapeutic agent can be increased "considerably" by proper timing of its administration.

Klevecz and his colleagues at the Beckman Research Institute at City of Hope have studied the proliferation of cancer cells in 31 patients with ovarian cancer. The experiment "represents the first around the clock analysis of human tumor cell proliferation in vivo and provides the potential for simultaneous comparison of normal and tumor cell proliferation." The analysis can also be used to "tailor treatment in each individual to the times of maximum growth of tumor cells," he said. "A comparison of standard cytological pathology with flow cytometry suggests that in some instances the detection of tumor cells depends on the time of day that the sample is taken."

The protocol involved saline irrigations of the abdominal cavity in patients who had undergone surgery for ovarian cancer. Approximately one liter of saline lavage with suspended cells was obtained every one or two hours for the first 24 hours, then every four hours for the next 24, with decreasing frequency thereafter. The cells in the saline washings were analyzed by flow cytometry for propipdium iodide fluorescence (DNA contents hypo-PI), as well as ethonol fixation. The cells were found to display circadian and higher frequency rhythms in the fraction of cells in "the proliferative protions of the cell cycle (S or S+G2 fraction)."

In ovarian cancer, the time of the most active tumor proliferation "appears to be bimodal with respect to peaks in S phase percentage and partially out of phase with the reported proliferation in human bone marrow and epidermis," Klevecz said.

Klevecz found significant rhythmic changes in the fraction of cells in S phase in all but two of the around the clock analyses. Most showed eight to nine hour, 12 hour or 24 hour rhythms in proliferation, with the percentage of cells with DNA content greater than the 2C (G1) value by P1 staining varying from less than 1% to more than 35%. The maximum in the number of cells in S+G2 occurred in the late evening and again in the early to midmorning hours. The minimum occurred most often between noon and 4 p.m. with some variation in relative amplitude and mean value of S phase from patient to patient. "This finding may offer one or two windows of four to six hours time each day when the tumor may be preferentially treated with reduced toxicity to normal tissues," he said.

When data from all the patients were pooled, Klevecz found an apparent 12 hour rhythm.

Klevecz pointed out that the second proliferative peak of the cancer cells was about 10 p.m. which is "perilously close" to the time when normal cells proliferate, but that the first peak in the morning is far enough away from the proliferative peak of the normal cells.

A combination of immunofluorescence in conjunction with DNA specific stains enables investigators to obtain a much better estimate of S phase fraction and total tumor cells in the washings.

Although "the mechanism generating these rhythms is unknown, it should be noted that in animals, from unicells to mammals, there is accumulating evidence that expression of circadian rhythmicity can be compromised by genetic manipulation, physiological stress or destruction of tissue integrity," Krevecz reported. "When this occurs the circadian clock is uncounted and higher frequency modes of oscillation predominate. This suggests that the fundamental clock is a high frequency oscillator whose period is an integral submultiple of the circadian clock."

William Hrushesky of the Univ. of Minnesota has reported on the potential value of adjusting drug dosages to circadian rhythms at previous ACS science writers seminars and elsewhere.

Diet Changes Can Be Tested In Few Months, MSK's Martin Lipkin Says

Proliferative indices may be used as a rapid assay system to test the preventive effect of dietary interventions on a population in a matter of months, Martin Lipkin, head of the Gastrointestinal Cancer Research Lab at Memorial Sloan-Kettering, said at the Science Writers Seminar.

The use of intermediate biomarkers such as cell proliferation makes it possible to study preventive measures such as various dietary regimens in stages, Lipkin explained. For example, in persons at high risk for colon cancer, the decrease of proliferation of cells lining the colon to a normal level "resembles the more healthy normal situation" found in persons at low risk for the disease, he said.

Lipkin noted that a common hyperproliferative abnormality is found in all preneoplastic gastrointestinal tissues studied--colon, stomach and esophagus. Other abnormalities of cell differentiation are being identified by both immunological and cloned gene probes in biopsy specimens.

Lipkin has been developing additional markers of preneoplastic cell differentiation. He noted that several investigators have shown that oncofetal gene functions are derepressed or reactivated during carcinoma evolution, with some of these occurring during early preneoplasia. Lipkin's findings "have suggested that expanded gastrointestinal stem cell populations with impaired cell differentiation are present in precancerous diseases of the gastrointestinal tract." He is currently developing "multiple markers of preneoplasia in colonic, gastric and esophageal cells for improved identification of our high risk subjects. These multiple markers also will make it possible to measure the effects of specific dietary interventions that attempt to inhibit the development of tumors."

In addition to proliferative abnormalities in subjects at increased risk for colorectal cancer, changes in expression of specific DNA sequences have been identified in the cells of subjects during stages of abnormal cell development leading to colonic cancer. Cloned sequences associated with different; stages of colonic tumor progression has begun, Lipkin reported.

Using short term assays to determine the success of dietary intervention in persons at increased risk, Lipkin and his colleagues have been able to modify the proliferation of colonic epithelial cells in subjects at increased risk for colon cancer, "from a profile characteristic of high risk to one of low risk," he said.

A recent MSK study used the markers to analyze modifications that might be induced by dietary interventions. The study examined the effect of supplementary dietary calcium on cell proliferation in the colon of 10 persons at increased risk for colon cancer using the proliferative indices as a rapid assay system to test the effect of dietary intervention.

The frequency and distribution of proliferating epithelial cells in the colons of the subjects at increased risk for familial colon cancer was studied before and after oral supplementation of their conventional diets with 1200 mg daily of calcium carbonate for a two to three month period.

Before calcium supplementation, the profile of distribution of proliferating epithelial cells in the colonic crypts was comparable to that previously observed for individuals affected by familial colon cancer, Lipkin said. Following calcium supplementation, however, epithelial cell proliferation was significantly reduced, yielding an altered colonic crypt profile approaching that previously observed in subjects at low risk for colon cancer. **These findings indicated that oral calcium supplementation induced a more quiescent proliferative equilibrium in the colonic mucosa of high risk individuals, similar to that observed for patients at low risk for colon cancer."**

Those findings were supported by a study at M.D. Anderson Hospital. "We believe that addition of calcium to the diet may modify the damaging effect of fat and help to prevent the development of colon cancer," Michael Wargovich reported at the meeting. He is assistant professor of cell biology and assistant cell biologist at MDA.

Investigators believe that once digested, dietary fats assume a chemical form that is injurious to the cells of the colon, which then proliferate to replace damaged or lost cells. "A chronic assault of fats in this state on the colonic cell may be the basis of promotion of carcinogenesis by dietary fat," Wargovich said.

Much of his current work focuses on anticarcinogenic substances in garlic and onions, which contain substantial amounts of organic suflides. Noting that sulfur compounds "may turn out to be rather important in inhibiting cancer," Wargovich reported that "diallyl sulfide, one of the major sulfides in garlic. . . has been shown in our hands to inhibit some of the earliest events in the development of experimentally induced cancer of the colon." The sulfide can also stimulate the body to detoxify car-

cinogens, the MDA studies have found, Wargovich noted.

An experiment currently in progress there will attempt to answer whether garlic prevents cancer. Wargovich hopes to report the findings this spring on the animal study, which will look at the inhibition of colon cancer. The experiment will compare four groups: one which receives diallyl sulfide, the second which receives diallyl sulfide and a carcinogen, the third which receives only the solvents used to administer the compounds, and the fourth group which receives the carcinogen alone. Groups will be measured against the one receiving the carcinogen alone.

Another development reported at the meeting is that of a laboratory system to study human papilloma viruses. "Our laboratory has recently orginated a new approach to the test of the hypothesis that human papilloma viruses contribute to the development of cervical cancer," John Kreider, professor of pathology and microbiology at Pennsylvania State Univ. reported.

The new system represents "an important advance in the study of the role of papilloma viruses in the development of human cervical cancer," Kreider said. "For the first time, the early stages of the process can be reproduced under controlled, laboratory conditions."

Kreider emphasized that investigators can now directly test the interactive roles of a number of agents in the causality of human carcinoma of the uterine cervix. For example, the importance of participating cofactors such as the human papilloma virus and cancer producing agents in cigarette smoke can be treated together. The system offers no risks to patients nor does it create ethical dilemmas, he said.

The new system offers "unparalleled opportunities to study the tretment of these diseases" and the effectiveness of agents such as interferon that prevent or inhibit the infection by papilloma viruses, Kreider said.

Because the viruses multiply in the infected grafts, they may be isolated from those tissues and the proteins that comprise their coatings could be used as the basis for protective vaccines, he suggested. Since similar vaccines can prevent papilloma virus infections in animals, human papilloma virus vaccines could prevent the uterine cervical infections and possibly the cancer.

New discoveries about lymphotoxin and its possible relationship to acquired immune deficiency could help develop treatment strategies or prevent development of the symptoms in their early stages, one investigator told the seminar.

Nancy Ruddle, associate professor of epidemiology and public health at Yale Univ. School of Medicine, said that the trans acting protein of HTLV-3 kills cells by inducing them to make lymphotoxin, which in abnormally high quantities results in the cell's self destruction. The role of lymphotoxin is being examined particularly as it relates to two manifestations of AIDS--depletion of the T4 subset and cachexia.

While noting that the virus HTLV-3 itself does not contain information to cause the devastation it wreaks on the immune system, the genome codes for a protein that can function as a trans action transcriptional activator (TAT), she reported. The protein most likely activates cellular genes to code for higher levels of proteins that would normally be produced by the cells. These proteins would normally be under tight regulation. Ruddle suggests that "it is possible that the TAT gene of the virus activates a cellular gene whose product kills the cells," adding that "the best candidate for a normal T cell product that could kill the cells that produce it is lymphotoxin." T8 cells are not infected by the virus because they lack the viral receptors,which appears to be the T4 molecule itself "and one would not expect T8 cells to be killed if their lymphotoxin genes were not activated by the virus. This is in fact the usual observation in AIDS, that is a selective depletion of the T8 subset."

Although not normally detectable in the serum, lymphotoxin might be present in the circulation in a situation in which it is not under normal regulation and is being produced at high quantities in a constitutive manner. Noting that lymphotoxin "could also manifest itself at sites distant from its production," she said "the cachexia observed in AIDS patients may be due to circulating high levels of lymphotoxin which. . . inhibits production of lipoprotein lipase."

Treatment possibilities could include substances such as cyclosporine which inhibit activated T cell production of IT, or substances that interfere with IT's activity. Agents that block target cell IT receptor are potentially useful.

Where did this come from?

Wisconsin Investigators Develop New Tool To Cut DNA At Any Desired Site

A new biochemical tool developed at the Univ. of Wisconsin (Madison) Medical School will enable genetic engineers to slice DNA at any desired site on its long chain, a feat never before possible, UW scientists have reported.

Molecular biologist Waclaw Szybalski of the McArdle Laboratory for Cancer Research and Anna Podhajska of Gdansk, Poland, said they have found a way to custom design the genetic engineers' "chemical scissors" to cut any part of DNA with razor sharp precision. Szybalski predicts the new technique will improve methods for locating unidentified genes, for diagnosing genetic diseases, for transferring genes between organisms and for producing purer biochemicals, such as hormones, from genetically engineered microbes.

"It's a dream come true for enzymologists and molecular biologists who have always wanted a way to tailor their tools to particular tasks," Szybalski said. He calls his discovery the "universal restriction enzyme."

Previously, scientists could cut DNA at only a limited number of sites for which they had the necessary scissors, or restriction enzymes.

As they occur in nature, restriction enzymes can attach to and cut through only about 100 of the millions of kinds of links in DNA's long chain of subunits, called nucleotides. This has meant that a snipped out piece of DNA may contain the desired subunits, but may also include long tails of unwanted nucleotides that complicate and sometimes thwart genetic engineering efforts.

Using a novel approach and a DNA synthesizer, popularly known as a "gene machine," Szybalski developed an "adapter molecule" that directs a single restriction enzyme to cut any specified DNA site.

"It was surprisingly easy once I got the theory worked out," Szybalski said. "up until now we've had to use a whole toolbox full of highly specialized but very limited cutting tools. Now we have a single, universal tool that can be easily adapted to any cutting task. Being able to cut DNA at any site can mean the difference between whether or not certain genetic engineering activities are done easily or not at all.

Szybalski's discovery is based primarily on work with a restriction enzyme called FokI, which reacts with a particular nucleotide sequence. The sequence includes a "recognition site" to which the left arm of FokI attaches, and exactly nine nucleotides away, a "cut site" to which the right arm attaches and through which it slices.

An important feature of FokI is that its DNA slicing activities are only triggered when it is anchored to double stranded DNA.

"A single strand won't do," Syzbalski said. "The complementary pairs of nucleotides found in DNA's double helix must be present at both the cut and the recognition sites, or FokI won't cut."

This in fact was a key to the creation of the universial restriction enzyme.

Szybalski reasoned that if he could permanently anchor the enzyme's left arm in a kind of "portable" recognition site, he could then manipulate the right arm to cut a variety of sites.

To do this, Szybalski and Podhajska created a special DNA adapter molecule. Its left end consisted of the double stranded recognition site. Its right end, nine nucleotides down the line, consisted of a single stranded sequence of DNA. The molecule, Szybalski said, looks like a hairpin with uneven ends.

"The right end is the variable part of the molecule," Szybalski said. "Here we attach nucleotides that are the exact complement, or opposite half, of the target DNA we want to cut. When FokI and the adapter are combined, FokI latches onto the adapter and all connections at the recognition site are completed. That site is primed to go. But the cut site is still single stranded and is not yet chemically complete at that point. It needs a complementary strand."

Completion occurs when the enzyme adapter complex is mixed with a single stranded chain of target DNA. As the nucelotides of the enzyme adapter's right arm seek out and bind to their opposites on the target DNA, the chemical equation is complete. The enzyme has a complete "cut site" and slices through the now double stranded section of the target DNA.

By altering the nucleotides on the adapter's right arm, Szybalski can program the enzyme adapter complex to cut any complementary link on a DNA chain. He added that it is a relatively simple process to separate normally double stranded DNA into single strands. The report appears in the winter issue of the journal, "Gene."

Program Announcement

Prevention and cessation of use of smokeless tobacco
Application receipt dates: June 1, Oct. 1, Feb. 1

The Smoking, Tobacco & Cancer Program of NCI is interested in supporting studies designed to develop and evaluate the effectiveness of interventions to prevent the onset and reduce the prevalence of use of smokeless tobacco in the U.S. The proposed studies should seek to identify patterns of smokeless tobacco use and the primary factors influencing such use; develop and evaluate intervention strategies to reduce the incidence and prevalence of smokeless tobacco use; and develop and evaluate assessment procedures to determine the long term effectiveness of these intervention strategies.

The purpose of this program announcement is to solicit applications from qualified investigators interested in developing innovative intervention programs focused on the use of smokeless tobacco and determining the long term effectiveness of these programs on the prevention and cessation of smokeless tobacco use. The focus of the studies envisioned must be on the long term effectiveness of interventions. It is anticipated that studies funded under this PA will be phase 3 (for the purposes of this PA, controlled studies of cancer control interventions in sizeable groups which may not, however, be representative of the larger population) and phase 4 (interventions designed and carried out within a large and defined population in such a way that the results obtained are representative of results in large target populations).

It is recognized that there are substantial gaps in knowledge concerning use of smokeless tobacco which may be essential to the development of an effective and durable intervention program. In particular, little is known about the demographics of users and those at risk for use, patterns of use, biological markers of use, factors influencing use, and the relationship to use of other forms of tobacco, particularly cigarettes. Therefore, applicants will have the option of using a phase in approach in which, during the first year, data describing the target population, prevalence, and patterns of use are obtained, unless such data are already available, and proposed interventions are pilot tested. At this point interventions would be initiated on a full scale. Information collected during the first year could be used to modify and adapt the proposed interventions as needed. In subsequent years interventions should be expanded with a major focus on evaluation of the interventions' effectiveness.

It is important that data collected in the studies funded under this PA be comparable so that comparisons can be made of patterns of smokeless tobacco use in different geographic and demographic populations. For this reason some standardization of data collection techniques and instruments will be encouraged. All funded investigators will meet with NCI staff as a group periodically to discuss appropriate measures for assessing use of smokeless tobacco, tc share informal progress reports, and exchange information and ideas. Budgets should include travel expenses from the home institutions to Bethesda for the principal investigator and one coinvestigator to attend two two day meetings each year for those purposes.

objective of these studies is to develop intervention strategies and to evaluate their effectiveness in preventing or reducing the prevalence of smokeless tobacco use. No restrictions are placed on the type of interventions, including the use of oral exams or the involvement of dentists and oral hygienists to deliver interventions. Any population subgroup may be chosen for study provided there is reasonable evidence that it contains a sizeable number of smokeless tobacco users or individuals who are at risk for initiating use (e.g, targeted by tobacco advertising; observed trends toward increased use; use by an immediately older cohort).

Prospective investigators should note that the outcome measure of these studies should be smokeless tobacco use, not cancer incidence/mortality, and that the desired overall outcome of studies eventually supported through this PA are interventions that are cost beneficial, cost effective, durable in their effects and readily adoptable by others with only those modifications that are necessary for a broad community/population impact.

Awards will be made as reserch project grants. The planning, direction and execution of the proposed research will be the responsibility of the applicant. The total project period should not exceed five years. Where more than five years is required, and the case is made for such, the possibility for longer studies will exist through competing renewal grant applications.

Consideration will be given to researchers' willingness to interact and cooperate with NCI to facilitate the Institute's goals for reductions of cancer morbidity and mortality.

Each application submitted in response to this PA will be reviewed by an appropriate panel of NIH and the National Cancer Advisory Board. All applications recommended for approval will compete with other regular RO1 approved grant applications for available funds. Applications must be responsive to this PA, in the sense of being directed towards the attainment of the stated programmatic goals. The factors considered in evaluating each response to this PA will be:

*Scientific merit of the research approach, design and methodology.

*Scientific and technical significance and originality of the proposed research.

*Research experience and/or competence of the PI and staff to conduct the proposed studies.

*Adequacy of time (effort) which the PI and staff would devote to the proposed studies.

*Relevance and appropriateness of the specific target population and assurance of its accessibility.

*Identity of sources of data, intervention materials, etc. and procedures for their analysis and assurance as to their accessibility.

*Adequacy of steps taken to optimize and fully evaluate the durability of the intervention effect.

*Likelihood of the intervention to be readily adoptable by others.

*Generalizability of the findings to large segments of the population.

*Reasonableness of the proposed budget.

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