DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

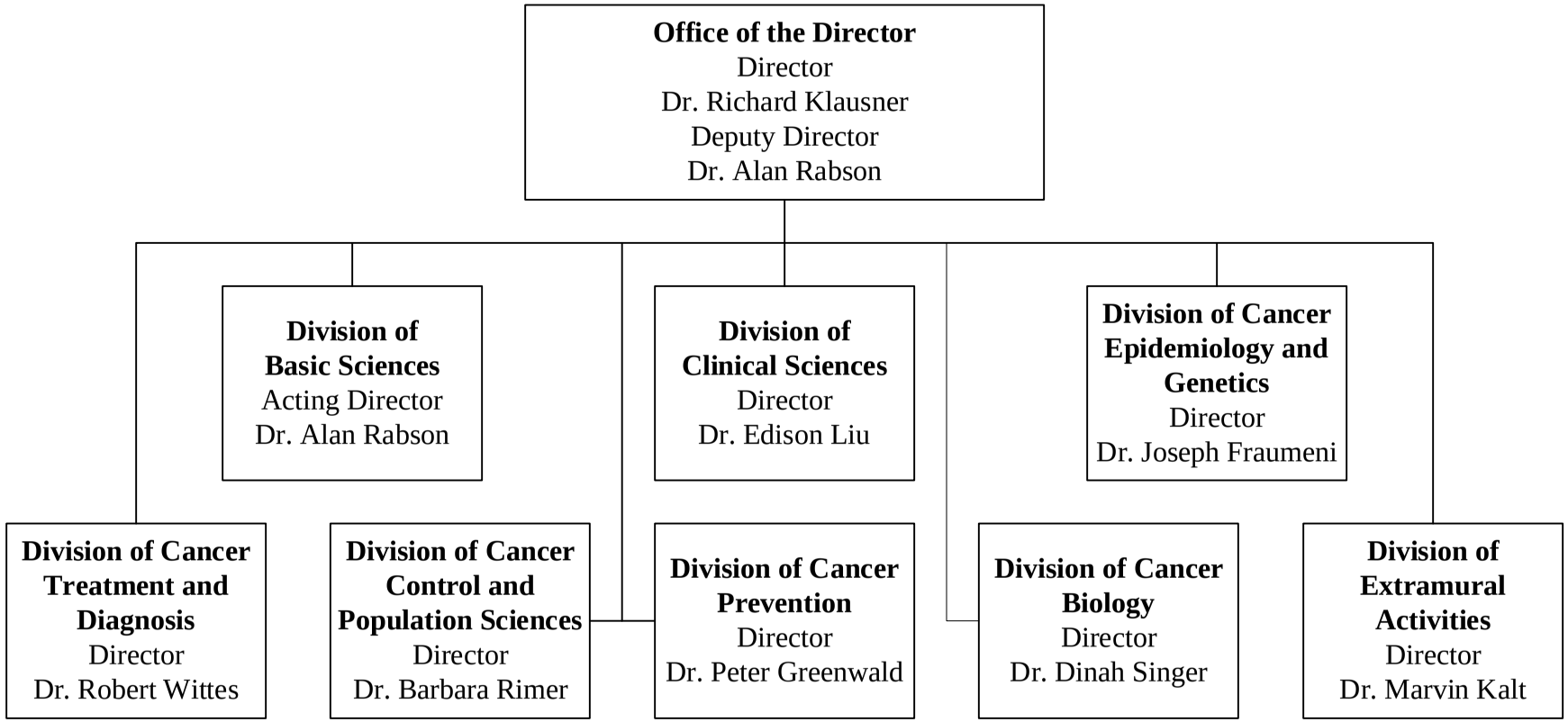
National Cancer Institute

FY 2001 Budget — Page No.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer, [$3,332,317,000] *$3,249,730,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, 2000, as enacted by Section 1000 (a)(4) of the Consolidated Appropriations Act, 2000 (P.L. 106-113)]

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation 1/

Source of Funding	1999 Actual	2000 Estimate	2001 Estimate
Appropriation	$2,927,187,000	$3,332,317,000	$3,249,730,000
Enacted Rescission	($1,940,000)	($17,763,000)	
Subtotal, Adjusted Appropriation	2,925,247,000	3,314,554,000	3,249,730,000
Real transfer to:			
Other NIH Institutes through the NIH Director's one percent transfer authority	(6,259,000)	---	---
Other HHS Agencies through Secretary's One Percent transfer authority	(931,000)	---	---
Comparative transfer to:			
Other NIH Institutes as a result of a change in assessment formula for Clinical Center funding	(23,881,000)	---	---
Other NIH Institutes as a result of a change in assessment formula for Central Services funding	(2,606,000)	(2,867,000)	
Office of AIDS Research, NIH for HIV activities	(234,653,000)	(244,494,000)	---
Subtotal, adjusted budget authority	2,656,917,000	3,067,193,000	3,249,730,000
Unobligated balance, lapsing	(7,000)	---	---
Total obligations	2,656,910,000	3,067,193,000	3,249,730,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1999 - $19,388,000; FY 2000 - $20,000,000; FY 2001 - $20,641,000

Excludes funding for HIV activities included in the Office of AIDS Research: FY 2001 - $255,342,000

Excludes $32,284,000 in FY 1999 and $25,000,000 in FY 2000 for royalties.

JUSTIFICATION

NATIONAL CANCER INSTITUTE

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 1999 Actual		FY 2000 Estimate		FY 2001 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2,393	$2,656,917,000	2,857	$3,067,193,000	2,908	$3,249,730,000	51	$182,537,000

This document provides justification for FY 2001 non-AIDS activities of the National Cancer Institute (NCI). Justification of NIH-wide FY 2001 AIDS activities can be found in the NIH section entitled, "Office of AIDS Research (OAR)."

INTRODUCTION

As we stand on the threshold of the 21st century, we are learning more each day about how cancer develops in the human body, about the ways that genes direct the behavior of cells and interact with environmental agents to cause cellular malfunction and disease, and about how to harness advanced technologies for more precise cancer research analysis, earlier detection, and more accurate diagnosis. Advances in our understanding of cellular activity hold promise for treatments that target specific steps in cancer development. New discoveries of inherited mutations provide clues to the causes of breast and prostate cancers. Prophylactic surgery and preventive agents with fewer side effects have potential for women at high risk to postpone or prevent breast cancer. Advanced technologies for data collection and tracking are allowing researchers to more fully understand disparities in cancer treatment delivery and outcomes. *In vivo* imaging of tumors in mice show promise for the non-invasive detection of very small tumors in humans. Results of a recent study on the interactive effects of cigar smoking and alcohol consumption have implications for our understanding of cancers of the upper aerodigestive tract and parts of the throat. The focus at the NCI continues to be on increasing survivorship and on enhancing the quality of life for survivors through less debilitating treatments, shorter hospital stays, fewer after effects, pain management, and general ability to lead more active, normal lives.

Despite our advances, cancer continues to be a major health problem, and for many Americans, it remains the most feared of diseases. The incidence of melanoma has been rising about three percent per year. Incidence rates for non-Hodgkin's lymphoma continue to rise inexplicably. Adolescents are smoking and using tobacco products at a troubling rate, and this trend may well reverse the currently falling rate of lung cancer. In addition, the burden of cancer still falls

disproportionately on certain racial, ethnic, and socioeconomic groups in our society. Although we have made real and lasting progress against the disease, it is critical that we continue to push forward toward our ultimate goal – the prevention and cure of all forms of cancer.

The proposed NCI Budget for Fiscal Year 2001 provides for research funding, supports training of the next generation of scientists, and enables more effective communication of cancer information. New initiatives in molecular biology will enable us to identify compounds that prevent or combat cancer. Discovering how and why elements in tobacco smoke target particular genes and how tobacco-induced cellular damage initiates and promotes cancer development will help us better understand why some people are more vulnerable to tobacco's harmful effects. Interdisciplinary research on and practical application of communications technology will enhance understanding and address the needs of disparate populations. Continued initiatives to more fully assess our Nation's cancer burden will: improve our ability to describe the cancer burden across a broader spectrum of the population; expand data collection to include information on screening practices, treatment options, and patterns of care; and develop methodological tools to expand the reach of our surveillance efforts. NCI is also leading a DHHS-wide initiative to ensure that all Americans receive the highest quality of cancer care. And, we will continue work to better understand cancer-causing genes and environmental factors, promote innovations in imaging technology, develop mechanisms to encourage application of new discoveries and emerging technologies, build new research technologies, and foster the convergence of ideas from traditional and alternative approaches through the NCI Office of Cancer Complementary and Alternative Medicine.

NCI's role is to provide the vision, creative environments, and diverse resources needed to ensure a smooth flow between the increasing number of discoveries and advances in cancer research and the scientific community's ability to apply these findings to prevent and treat the many forms of cancer. We need mechanisms that will promote and reward innovative thinking, enhance cross-fertilization among scientific disciplines, and enhance collaborations among government, academia, and industry. Each day, across the United States and around the world, thousands of NCI-funded researchers and clinicians address cancer biology, causation, risk, prevention, detection, treatment, and survivorship, bringing us closer to the day when cancers are an uncommon and easily treatable set of diseases. Our course now is to sustain proven, productive research programs, seize extraordinary opportunities made possible by our previous research discoveries, and build the capacity that allows the scientific community to rapidly apply new discoveries and emerging technologies to benefit human health.

SCIENCE ADVANCES

Cancer researchers have made important progress in a number of research areas during the past year. Some of the most compelling advances are described below.

New Approaches to Pathogenesis – Creating Human Cancer Cells
After years of study, we know that cancer arises through a multistep process involving the accumulation of genetic alterations, abnormalities that enable a cell to override the normal mechanisms that control cellular proliferation and divide on its own schedule. Despite this important knowledge, scientists have struggled for more than 15 years to create human cancer

cells in a cell culture dish. Some scientists have used chemical or physical agents to transform normal cells into cancer with limited success. And, although a team of researchers showed more than a decade ago that changes in two specific genes promoting cell growth caused rodent cells to become cancerous, similar experiments using human cells failed. Until now, no one has been able to identify the minimum number of defined genetic events needed to transform a human cell from one that is normal to one that will continue to proliferate indefinitely.

In a striking achievement, a team of NIH-supported scientists recently converted normal human cells to tumor cells in a culture dish by altering the expression of a defined set of genes, changing at least four pathways in the cell. Using two different cell types to ensure that the observed effects were not limited to a particular type of cell, the scientists first artificially stimulated the expression of the telomerase enzyme, hTERT, which maintains telomere length (pathway 1). Telomeres, specialized structures that define the ends of chromosomes, become increasingly shorter every time a cell divides; such shortening may serve to limit a cell's lifespan. Stimulating expression of hTERT overcame telomere shortening and allowed the cells to proliferate indefinitely. They then added two familiar oncogenes: an activated *ras* gene found in many human tumors which stimulates cellular growth (pathway 2) and a gene from the simian virus 40 (SV40) retrovirus that encodes for the large T protein. This protein transforms normal cells infected with SV40 by inactivating the cellular pathways controlled by the p53 and retinoblastoma tumor-suppressor proteins (pathways 3 and 4). The delivery of all three elements – hTERT, an activated *ras* oncogene, and the large-T protein – transformed normal human cells grown in cell culture, causing them to behave as cancer cells. Because all three elements were needed to convert the normal cells, the scientists concluded that mutations activating telomerase cooperate with other alterations in oncogenes to transform normal human cells to cancerous ones. In addition, when the transformed cells were injected into mice, the animals developed tumors, confirming that these cells developed in a cell culture system were indeed capable of producing tumors in living animals.

The ability to introduce specific genetic alterations to transform normal cells provides the exciting opportunity to define the biochemical pathways in the cell that must be disrupted in the development of cancer. Such information will open new avenues for exploring the roles of various cellular pathways that become disrupted and for determining the sequence events that must occur as cancer develops. For example, using the approach developed by these investigators, we can now determine whether the *ras* oncogene must be activated before or after the introduction of SV40 for cancer to develop. Such information will be useful for developing treatments that target specific steps in cancer development.

New Preventive Strategies Against Disease

Scientists have been seeking to learn how to prevent cancer for decades. Through these efforts, we have identified many ways to help lower our risk of developing certain cancers and discovered agents that can help to prevent the disease. Today, our increasing knowledge of the cellular and genetic changes that lead to cancer, and the factors that cause these changes, is enabling us to create targeted preventive strategies designed to stop the process of cancer development before it begins.

Prophylactic Surgery for Breast Cancer Risk Reduction
Today, when a woman is faced with the knowledge that she has an inherited predisposition to breast cancer her choices include close observations to ensure early detection, prevention with tamoxifen, or prophylactic surgery to remove breasts and/or ovaries before disease develops. While data suggests that tamoxifen may lead to a 49 percent reduction in the incidence of primary breast cancer in women at a high risk for the disease, little data is available on surveillance and prophylactic mastectomy interventions. Despite this lack of scientific data, some women who are at high risk of breast cancer make the difficult decision to have both breasts surgically removed, a procedure known as bilateral prophylactic mastectomy (PM).

Two recent studies provide some exciting new information on prophylactic surgery in the reduction of breast cancer risk in women at high risk for the disease. Researchers studied the long-term outcomes in women with a family history of breast cancer who had undergone PM at the Mayo Clinic between 1960 and 1993. In this study, PM was associated with a reduction in incidence of the disease of at least 90 percent.

In a separate study, researchers explored whether surgical removal of the ovaries (prophylactic oophorectomy or PO) lowers the risk of breast cancer among women at inherited risk of breast and ovarian cancer due to *BRCA1* mutations. This study compared the incidence of breast cancer in women with *BRCA1* mutations who had undergone PO with that of women with similar mutations who had not had a PO. PO was found to reduce the risk of breast cancer by about 40 percent for all women with *BRCA1* mutations and that risk reduction increased over time from surgery. Prophylactic removal of the ovaries on completion of their childbearing years has been recommended for women at inherited risk of breast and ovarian cancer. This data provides additional information on the use of PO in reducing risk of breast cancer for women at high risk.

These studies are of major importance to the health care of women at markedly increased risk of breast cancer due to an inherited mutation of *BRCA1* or a family history of the disease. Together the studies add to our body of knowledge on reducing the risk of breast cancer among women with a genetic predisposition to the disease. While these findings are provocative, further research is needed to replicate them and to explore other aspects of prophylactic surgery, such as optimal surgical techniques, hormone replacement and the use of preventive agents following surgery, and the public health implications of these interventions among targeted risk groups.

Tamoxifen as Agent for Breast Cancer Risk Reduction
In 1992, the NIH-supported National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented the precedent-setting Breast Cancer Prevention Trial (BCPT) to determine whether tamoxifen (Nolvadex®, Zeneca Pharmaceuticals, Wilmington, Delaware), a drug that had been used since the 1970s to treat breast cancer, would prevent breast cancer in women at increased risk of developing the disease because of age or personal or family history. Researchers on the BCPT demonstrated a 49 percent reduction in breast cancer incidence among the high-risk participants who took tamoxifen, a drug used for the past two decades to treat breast cancer. Women on tamoxifen also had 50 percent fewer diagnoses of noninvasive breast cancer, such as ductal or lobular carcinoma in situ. Tamoxifen was also found to increase the women's chances of three rare but life-threatening health problems: endometrial cancer (cancer of the lining of the

uterus); pulmonary embolism (blood clot in the lung); and deep vein thrombosis (blood clots in major veins).

Researchers are now creating and testing a second generation of breast cancer prevention agents, such as raloxifene, which may help to reduce the risk of the disease without some of tamoxifen's potential side effects. In 1999, the NSABP launched the Study of Tamoxifen and Raloxifene (STAR), a trial that is comparing the two drugs' abilities to reduce the frequency of the onset of breast cancer in high-risk, post-menopausal women as well as comparing the side effects of the two drugs. Approximately 22,000 women will participate in this study.

The results of the BCPT provide evidence that the risk of human cancer can be reduced with a pharmacologic intervention (in this case, tamoxifen). The BCPT also showed that large chemoprevention trials can accrue participants and be completed successfully. The study's findings provide an alternative to "watchful waiting" or surgery for women who are at high risk of developing breast cancer. These findings challenge health care providers involved in the care of breast disease to develop a better understanding of risks and benefits in healthy populations and to be able to counsel "at-risk" women regarding available options.

New Avenues for Development of Therapeutics
Ultimately, the purpose of understanding tumor biology and cancer genetics is to discover effective ways to halt and reverse the progression of cancer. Researchers are pursuing a number of promising avenues in this study area. Recent advances in two promising areas, vaccine development and multimodality therapy, are discussed below.

Therapeutic Vaccine Development for B cell Lymphoma
Cancer vaccines are a promising form of biological therapy currently under study. Like other forms of biological therapy, vaccines work against cancer by creating an immune response in the body against foreign invaders (antigens). Recently, NIH researchers launched a small clinical trial to determine the effectiveness of a novel vaccine against B cell lymphoma, a common blood-cell tumor that strikes an estimated 41,000 Americans each year.

In the small, phase II (efficacy) trial, the researchers developed vaccines for each patient by obtaining the receptor molecule (tumor antigen) from the patient's own tumor then coupling it to a carrier protein capable of creating an immune response. Then, to heighten the immune response provoked by this antigen/protein combination, a second immune system boosting substance, granulocyte colony-stimulating factors (GM-CSF), was added. GM-CSF stimulates blood cell production and is capable of eliciting a strong response from T cells, the white blood cells that orchestrate our immune system's response to foreign cells. When the vaccine combination was given to the patients, the GM-CSF and carrier protein provoked an immune system attack targeted to the antigen found on the patient's tumor. Researchers then tested each patient's blood for the presence of remaining microscopic disease by looking for chromosomal or molecular changes only seen in cancerous cells. Of the patients analyzed, 75 percent no longer showed signs of microscopic disease. Researchers achieved a high response rate to the B cell lymphoma vaccine while establishing a principle for therapeutic vaccine creation that may someday be applied to more common tumors such as prostate, breast, and lung cancers.

Chemotherapy Plus Radiation to Improve Survival of Patients with Cervical Cancer
Our ability to prevent cervical cancer through regular Pap (Papanicolau) smear screening tests has been a major public health success story in the United States. Even with the success of screening, an estimated 12,800 women are expected to be diagnosed with invasive cervical cancer in 1999 and about 4,800 women will die from it.[1] In the developing world, cervical cancer is the second leading cause of cancer deaths among women. About 400,000 cases are diagnosed annually world-wide, predominantly among the economically disadvantaged in both developing and industrialized nations.[2]

Up to now, surgery or radiation therapy alone has been considered the standard treatment for cervical cancer that has spread locally (within the cervix) or regionally (within the pelvis). Findings from five different large, randomized clinical trials show that women with cervical cancer who received both chemotherapy with cisplatin and radiation therapy, given at the same time, lived longer with fewer disease recurrences than those treated with radiation alone. Several hundred women were enrolled in each of the five trials, which were carried out by NIH's Clinical Trials Cooperative Groups in centers around the country. In three of the studies, women were randomly divided into groups, or "arms" that received either radiation alone or radiation plus concomitant chemotherapy (given at the same time as the radiation therapy). The chemotherapy agents used were cisplatin and 5-florouracil, also known as 5-FU (two studies) and cisplatin alone (one study). In all three trials, the proportion of women alive after about three years of follow-up was higher in the groups receiving chemotherapy plus radiation than in those receiving only radiation therapy. In two other studies, all patients received concomitant chemotherapy and radiation. However, the chemotherapy drugs differed between the arms. In one arm of each of these trials, the chemotherapy used was hydroxyurea while in the other arm, the chemotherapy included cisplatin. In both trials, the groups who received cisplatin had better survival rates. Although the trials vary somewhat in terms of stage of disease, dose of radiation, and schedule of cisplatin and radiation, they all demonstrate significant survival benefit for this combined approach. The risk of death from cervical cancer was decreased by 30 to 50 percent by concurrent chemotherapy and radiation treatments.

The findings from these five trials are likely to change the standard of care for invasive cervical cancer. In February 1999, NIH issued a Clinical Announcement to physicians, urging them to review the data from these trials and consider using cisplatin-based chemotherapy at the same time as radiation therapy in treating women with cervical cancer.

Genetic Medicine
Years of research focused on understanding how cancer develops have shown that cancer invariably involves altered genes and altered gene function. Genetic mutation, whether it is inherited or results from exposure to certain chemicals or viruses, alters the normal processes that a cell uses to regulate its actions. Once these processes are disrupted, control is lost and a tumor develops. Studies in cancer genetics are providing unprecedented insight into the development and evolution of cancer and are generating knowledge about the most basic processes involved in the onset of this disease. This knowledge will be critical to the

[1] American Cancer Society, Surveillance Research: *Cancer Facts & Figures 1999*, p. 17, 99-300M-No. 5008.99.
[2] D. Maxwell Parkin,, Paola Pisani, and Jacques Ferlay: "Estimates of the worldwide incidence of 25 major cancers in 1990," *International Journal of Cancer*, Vol. 80, No. 6, 827-841, March 15, 1999.

development of prevention and control strategies, early detection methods, and in some cases, more precise clinical intervention and management approaches. In the past few years, scientists have made remarkable progress in the study of cancer genetics, including breast, prostate, and colon cancer genetics.

Breast Cancer Genetics

Our understanding of the genetic factors that influence breast cancer risk continues to improve. Through research studies we have discovered that women who have inherited mutations in the *BRCA1* gene have a greatly increased risk of developing breast cancer compared to the general population. Other genes, however, particularly those involved in hormonal signaling, may modify *BRCA1*-associated age-specific breast cancer risk. Researchers studied the effect of a variation, repeats of the triplet nucleotide CAG, in the androgen-receptor gene associated with a decreased ability to activate androgen-responsive genes. They found that women with *BRCA1* mutations whose androgen receptor CAG triplet repeated 28 or more times were diagnosed with breast cancer significantly earlier than women whose CAG triplet repeated fewer than 28 times. These results support the hypothesis that age at breast cancer diagnosis is earlier among *BRCA1* mutation carriers who carry very long androgen receptor CAG repeats and suggest that pathways involving androgen signaling may affect the risk of *BRCA1*-associated breast cancer.

Prostate Cancer Genetics

Researchers have identified an alteration, or a region of deletion, on chromosome 8 (8p21) in approximately 80 percent of prostate tumors studied. This region also overlaps a region recently identified as a locus for familial breast cancer. Deletions were also found in 63 percent of precancerous prostate lesions, suggesting that abnormalities on 8p21 may be associated with early stages of prostate cancer development. A physical map of this region is currently being constructed, and researchers have begun analyzing candidate genes that reside in this area.

Colon Cancer Genetics

NCI-supported scientists recently identified a genetic mutation that may be responsible for over 11,000 (nine percent[3]) of the 129,000 colorectal cancer cases diagnosed in the U.S. each year.[4] The TbetaR-I(6A) defect, a mutant form of the Transforming Growth Factor Beta (TGF-b) receptor, is a new mechanism – found in both cancer patients and healthy individuals – that may increase a person's risk for cancer.

In a case control study, researchers compared blood samples taken from cancer patients and healthy volunteers. They observed that the TbetaR-I(6A) mutation was more common in people with cancer than in healthy people, suggesting that the mutation plays a role in the disease. People can inherit two copies of this receptor gene, one copy from each parent. A significant number of patients with colon cancer inherited either one or two copies of the mutation. Interestingly, a large number of cancer patients and healthy participants also had a single copy of the mutation, indicating that the mutation occurs in about 10 percent of the general population.

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[3] Boris Pasche, Prema Kolachana, Khedoudja Nafa, Jaya Satagopan, Ye-Guang Chen, Roger S. Lo, Dara Brener, Diana Yang, Laurie Kirstein, Carole Oddoux, Harry Ostrer, Paolo Vineis, Liliana Varesco, Suresh Jhanwar, Lucio Luzzatto, Joan Massagué, and Kenneth Offit:" TR-I (6A) Is a Candidate Tumor Susceptibility Allele," *Cancer Research* 59, p. 5678, November 15, 1999.

[4] American Cancer Society, Surveillance Research: *Cancer Facts & Figures 1999*, p. 9, 99-300M-No. 5008.99.

People who carried two copies of the mutation had the most pronounced risk for developing cancer, although the degree of added risk has yet to be determined.

The scientists have hypothesized that the TbetaR-I(6A) mutation may contribute to the development of cancer, particularly colon cancer, by hampering a cell's normal efforts to control cell growth. Under normal conditions, the TGF-b signaling protein binds to a receptor on the cell surface, setting in motion a cascade of intracellular events that carry the signal to the cell's nucleus to stop cell growth. The TbetaR-I(6A) mutation, however, slightly weakens the receptor, thereby interfering with the receptor's ability to respond properly to the TGF-b braking signal. In the development of cancer, tumors lose their ability to respond to the TGF-b signal and continue to grow uncontrollably.

The researchers are planning follow up studies to assess the risk for colon cancer or precancerous polyps in individuals who carry the receptor mutation. Although the investigators have cautioned that testing for the mutation should only be done at present for research purposes, this finding one day may help physicians identify at risk patients who should be closely followed for early signs of disease.

Bioengineering, Computers and Advanced Instrumentation
Powerful new tools for the laboratory and clinic are revolutionizing cancer research and care, enabling scientists and physicians to do their work more efficiently and expediently. Two of these tools, spiral computed tomography and near-infrared fluorescent imaging probes, represent significant advances in the cancer field.

New Screening Tool for Lung Cancer
Lung cancer, the leading cause of cancer death for men and women in the United States, claimed the lives of an estimated 158,900 people in this country in 1999 according to the American Cancer Society.[5] This troubling statistic stems in large measure from our limited ability to detect lung cancer at an earlier and potentially more curable stage. Using available detection methods, most people are diagnosed in advanced stages of disease and only slightly more than 12 percent survive five years. Survival improves dramatically, up to 70 percent, when the disease is identified and treated early. Clearly, an effective screening tool for lung cancer would enable early detection and reduce the number of lung cancer deaths, but until recently, none has been available to physicians. Annual chest x-rays, for example, have not been shown to be useful and alternative methods are too costly to be used for routine screening. Now, advances in imaging technology have led to the development of a promising technique, low radiation dose spiral computed tomography (spiral CT). Spiral CT can scan entire lungs from the neck to the diaphragm in less than 20 seconds – a single breath-hold. Rapid scanning minimizes radiation exposure and improves the detection of smaller lesions since they are not moving in and out of the field of view due to breathing. This new tool may prove to be the first screening method to find some types of lung tumors early and reduce lung cancer deaths.

In the Early Lung Cancer Action Project study, NIH-supported researchers recently tested the effectiveness of spiral CT as a screening tool for lung cancer. The 1,000 symptom-free

[5] American Cancer Society, Surveillance Research: *Cancer Facts & Figures 1999*, pp. 4 & 12, 99-300M-No. 5008.99.

participants of the study, considered to be at high-risk for lung cancer because of their age (60 years or older) and cigarette smoking history (a minimum of ten pack-years where a one-pack year is equivalent to one pack of cigarettes smoked every day for one year), were given baseline and annual spiral CT examinations. The researchers demonstrated that, compared to chest x-ray, spiral CT is a considerably more effective tool for detecting small non-calcified lung nodules and thus, for detecting lung cancer at an earlier and potentially more curable stage. Malignant tumors were detected four times as often with spiral CT as with chest x-ray, and stage 1 tumors were detected six times as often with spiral CT as with chest x-ray. This technology, however, may be less useful in clinical application for detecting central airway tumors, such as squamous cell carcinomas, and very rapidly growing carcinomas, such as small cell lung cancers.

Further research is needed to determine whether lung cancers detected through routine screening with spiral CT are actually more effectively treated and how the size of the tumor at the time of detection may affect the rate of cure. NCI plans to conduct a randomized clinical trial involving several thousand participants to determine the benefits and potential drawbacks of using spiral CT for screening. Routine, less costly screening with spiral CT may enable physicians to find lung cancer at an earlier and more curable stage, thereby reducing the number of lives lost to lung cancer.

In vivo Imaging of Tumors in Mice with Protease-Activated Near-Infrared Fluorescent Probes
Early detection of small tumors is a mainstay of successful cancer treatment. Cancers detected early, before they have had the chance to spread, are more easily treatable and more frequently curable than more advanced cancers. However, current methods for the non-invasive detection of small tumors are limited in their ability to distinguish small areas of abnormal cells from larger surrounding areas of normal tissue.

NIH grantees have developed a new method to more precisely image tumor cells. They injected tumor-bearing mice with a unique imaging agent composed of near-infrared fluorescence imaging (NIRF) probes coupled with a novel substance that moves efficiently into tumor cells. When the agent was internalized into cancer cells, enzymes within the cells “activated” the agent and caused it to fluoresce allowing for non-invasive detection. The agent was not activated in non-tumor cells. Using this technique, the investigators were able to image tumors smaller than 300 microns (three-tenths of a millimeter) in diameter. Although this new technique is in the early stages of development, and has yet to be tested in the clinic, it shows great promise for the non-invasive detection of very small tumors.

Health Disparities
More complete and accurate surveillance data and innovative approaches for using combined surveillance and Medicare data enhance our ability to track and analyze available information on cancer disparities. Our understanding of disparities in cancer is also enhanced through studies focusing on the basis for disparities in incidence of certain cancers such as prostate cancer, risks associated with specific life-style choices such as cigar smoking and alcohol consumption and disparities in survival that often revolve around societal factors.

Interpreting Emerging Patterns and Trends in Cancer

Cancer incidence rates declined approximately 0.9 percent a year between 1990 and 1996, and cancer death rates fell approximately 0.6 percent a year during the same period, according to a 1999 report of the NIH, the American Cancer Society, the Centers for Disease Prevention and Control, and the National Center for Health Statistics.[6] Their Report to the Nation outlined major cancer trends in the 1990s. The investigators noted that overall, cancer incidence and death rates have declined significantly since 1990. In particular, lung cancer rates for men (although not for women) appear to be on the decline. These trends are encouraging, but the investigators caution that unless recent upward trends in smoking among adolescents are reversed, lung cancer rates may begin to rise again.

NIH scientists have inaugurated the Cancer Surveillance Series of research articles that address the emerging patterns of cancer in various population groups in the United States, and explore the many elements (e.g., risk factors, screening, diagnosis and treatment) affecting these patterns at the national and regional levels. The series also publicizes the data sources and systems that are available for cancer surveillance research, and provides a forum for wide dissemination of the latest analysis and evaluation of cancer statistics in the United States. The series was inaugurated in June 1999 in the *Journal of the National Cancer Institute*. Summaries of the findings reported in that issue include the following:

- In a three-part article, investigators evaluated the incidence and mortality trends from prostate cancer and the impact of prostate-specific antigen (PSA) screening (a common blood test that frequently indicates the presence of prostate cancer), attribution bias, and other factors. They found that since PSA screening was introduced in the 1980s, the incidence of advanced prostate cancer has declined, as has the overall prostate cancer mortality rate, indicating that such screening is enabling earlier detection and *possibly* a sustained decline in the prostate cancer death rate. Investigators further report that some recently diagnosed patients who die of other causes may be mislabeled as having died of prostate cancer. Finally, they note that it is unlikely that the entire decline in prostate cancer mortality can be explained by PSA testing. The investigators note the complexity of the data and indicate that there is some evidence that PSA screening leads to a decrease in overall prostate cancer deaths, although alternative interpretations are possible.
- There was no substantial change in incidence for the major pediatric cancers, and rates have remained relatively stable since the mid-1980s. The modestly increased incidence reported in certain cancers was confined to the mid-1980s and probably reflected improvements in diagnosis or changes in reporting. Mortality rates declined steadily for all major childhood cancers due to dramatic improvements in treatments. However, those rates declined less rapidly for brain and other central nervous system cancers in children.
- Geographic patterns of lung cancer have changed considerably since 1950, and have generally coincided with regional trends in cigarette smoking. This finding indicates that

[6] Wingo PA, Ries LAG, Giovino GA, Miller DS, Rosenberg HM, Shopland DR, Thun MJ, Edwards BK: "Annual Report to the Nation on the Status of Cancer, 1973-1996, With a Special Section on Lung Cancer and Tobacco Smoking. Special Article," *Journal of the National Cancer Institute*, p. 675, Vol. 91, No. 8, April 21, 1999.

public health measures aimed at smoking prevention and cessation could be highly effective in reducing lung cancer rates.

Appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of disease. NIH uses its surveillance activities to identify key trends in cancer – both the good news (significant dips in cancer incidence and mortality) and the bad (an increase in smoking among adolescents). By interpreting these trends, NIH will be able to direct education and cancer prevention efforts where most needed.

Use of Combined SEER-Medicare Data

Cancer registries gather a wide variety of specific information on cancer patients that can be analyzed to identify health disparity trends in cancer incidence, mortality and patient survival. The Surveillance, Epidemiology, and End Results Program (SEER) is a continuing project of the NIH to collect cancer data on a routine basis from designated population-based cancer registries in various areas of the country. The geographic areas covered by the SEER Program's data base represent an estimated 14 percent of the United States population. The SEER-Medicare database links information from the cancer registries with Medicare-eligible persons reported to the SEER registries. The studies discussed here indicate that information linkages between cancer registries and other large sources of data can be important research tools.

In several studies using the linked SEER-Medicare data, researchers found that claims such as those collected by Medicare will capture 75 to 90 percent of cancer cases supported by the cancer registries, completeness varying by the type of cancer, although data from cancer registries remains an extremely important source of information. One study found that using the Medicare claims to determine if a person had a newly diagnosed breast cancer had significant limitations. Another found that using the Medicare data offers the potential to enhance the census and evaluation of adjuvant treatments, such as radiation therapy, that are supposed to be recorded by registries, but are sometimes missed as the care is provided in an alternate location.

The SEER-Medicare data were also used to examine the ways patterns of care differ between health maintenance organizations (HMOs) and fee-for-service (FFS) settings. By 1996, approximately 20 percent of the U.S. population, and about 14 percent of Medicare recipients, were enrolled in HMOs, a significant increase since 1980. In three studies, NIH researchers and grantees compared treatment and outcomes among Medicare recipients in HMOs and FFS settings.

- In the first study, researchers studied the care received by colorectal cancer patients within the geographic areas served by two large, not-for-profit HMOs. They found little difference in treatment and cancer-specific mortality between patients treated in HMOs and patients treated in the FFS setting.
- In the second study, researchers looked at the same geographic area and found that 10-year survival following a diagnosis of non-metastatic prostate cancer diagnosis was similar for men treated in each setting, although there were significant differences in treatment between the FFS and one of the HMOs.
- In the final study, researchers compared differences in stage and treatment for older women with breast cancer. The investigators found that women in HMOs were diagnosed at an

earlier stage. The use of lumpectomy for early-stage cancers was similar between HMOs and FFS, although the recommended radiation therapy following lumpectomy was more likely to occur in HMOs. The type of care received by women within HMOs varied widely – some HMOs had high rates of breast-conserving surgery, others had very low.

Given the variation in the type of care among HMOs, comparing HMOs as a group with FFS as a group may have limitations; however, as the number and types of health care plans continue to increase, it will be important to monitor the effects of alternative delivery systems on cancer detection and treatment.

The use of the combined SEER-Medicare data will allow us to conduct important research on treatment delivery and outcomes. The second set of findings reported here underscores the benefit of linking data from cancer registries with large sources of claims, such as the Medicare data, while the first set provides an example of how the combined data can be used.

Gene Mutation Linked to Prostate Cancer in African American and Hispanic American Men
Scientists have identified a genetic mutation that may explain the much higher rates of prostate cancer experienced by African American and Hispanic American men as compared to Caucasians and may provide clues to the cause of prostate cancer. Because prostate cancer is known to "feed" off male hormones, the team studied a gene that encodes the enzyme called steroid 5-alpha-reductase which controls aspects of hormone metabolism. They identified a simple mutation on the *SRD5A2* gene that occurred rarely in healthy African American and Hispanic American men but occurred much more frequently in men from those ethnic groups who had prostate cancer. The more advanced the cancer, the more likely this mutation would occur. This intriguing finding requires further evaluation and confirmation, but it identifies another new candidate gene for prostate cancer that may be especially important for specific ethnic groups.

Health Effects of Cigar Smoking
The sale of cigars in the United States has been increasing since 1993, reversing a 20-year decline in the rate of cigar consumption. The resurgence of cigar smoking may be attributed, in part, to the perception that cigars are safer than cigarettes. However, few data are available on the health effects associated specifically with cigar use, especially with regard to cardiovascular disease risk. In this study, 17,774 men ages 30 to 85 who were enrolled in the Kaiser Permanente health plan and were not cigarette smokers were followed through the end of 1995. Researchers found that cigar smokers, as compared with nonsmokers, were at increased risk for cancers of the lung and the upper aerodigestive tract (including the top of the throat, the nose, the larynx, and the esophagus), cardiovascular disease, and chronic obstructive pulmonary disease, independently of other risk factors for these diseases. Risks were greater among those who smoked five or more cigars a day compared to those who smoked fewer. There appeared to be a synergistic relationship between alcohol consumption and cigar use with respect to risk of cancers of the upper aerodigestive tract and parts of the throat. Far from being a "safe" form of recreation, cigars pose significant health risks to people who smoke them. Their increasing popularity is rapidly emerging as a troubling public health issue.

Cancer Survival Rates in Underserved Populations
Research is demonstrating that differences in cancer morbidity and mortality previously attributed to race are not due to supposed biological differences between populations or between the tumors individuals develop. Rather, these differences actually reflect the too-frequent biological and medical consequences of socially-defined race – socioeconomic status, educational level, and degree of access to high quality cancer care. NCI-supported researchers recently compared the outcomes of black and white patients with colon cancer enrolled in five clinical trials. They found, as other analyses of NCI clinical trials have, that equal treatment yields equal outcome, and that race is not a factor in cancer-specific survival when there is equal treatment. Data from NCI's Black-White Study of Cancer Survival showed that compared with white women, black women with breast cancer (as well as poor women) were less likely to receive appropriate treatment after diagnosis. They also are more often diagnosed at a later stage of disease and are less likely to have a regular source of health care. Similar disparities in appropriate treatment have been demonstrated between various population groups with prostate, lung, and cervical cancers. NCI studies are now focusing on determining the reasons for the differences in care.

NEW INITIATIVES

Molecular Targets of Prevention and Treatment
Until recently, scientists working to discover effective prevention and treatment agents have faced the formidable barrier of not knowing precisely what cancer is. With the evolution of molecular biology and the emergence of new technologies, however, we now are gathering remarkable knowledge about the nature of a cancer cell and the molecular changes that occur during tumors' development. This new knowledge of the differences between cancerous and normal cells is enabling us to understand and classify human tumors in terms of molecular changes and is providing us with a powerful new strategy to identify compounds, both natural and synthetic, that prevent or combat cancer.

The opportunity for targeted drug discovery has not evolved from advances in cancer biology alone; this opportunity also has been fueled by critical progress in several other areas. For example, using recently developed techniques in synthetic chemistry, chemists now can create in the laboratory enormously diverse collections, or libraries, of compounds that can be screened for possible anti-cancer effects. And, the recent biotechnology revolution is allowing biochemists a newly developed opportunity to mix and match genes to design synthetic proteins and thus, to create an entirely new class of compounds to be tested for anti-cancer activity. Advances in biotechnology also are making it possible to devise high throughput "smart" assays to rapidly and efficiently screen cell lines for the presence of genes, proteins, or entire pathways, and to screen potential agents for anti-cancer effects. Finally, refinements in imaging technology are allowing scientists to watch molecular processes within the cell as they occur with unprecedented vividness and accuracy – providing the potential to track a drug within the body or to visualize its immediate effects on cancerous cells and tissues. The convergence of all of these advances presents us with the opportunity to place discovery and development of cancer prevention and treatment interventions on a firm scientific footing.

To ensure our success in developing a whole new generation of cancer treatments and preventives, we need to create conceptual and functional links among discovery, development, and clinical testing of agents in completely unprecedented ways. As a first step, NCI plans to fund studies to identify and characterize molecular targets for drug discovery. For example, Molecular Target Discovery grants will fund efforts to identify, characterize, and validate cancer-relevant molecules or pathways that may be suitable targets for prevention or treatment discovery efforts. Once we have established the credentials of a molecule or pathway, we can exploit the most promising targets for drug design and high throughput screening efforts.

New tools and methods are needed to test the effectiveness of newly-developed, promising compounds. NCI plans to facilitate this effort by: working with expert organizations to help develop sensitive, high throughput assays for priority molecular targets to assess the effects of compounds on a target; assembling and curating a "Library of Libraries" – a rich collection of small molecule chemical libraries to complement NCI's existing respositories of natural product extracts and synthetic chemicals formatted for screening and widely available to researchers; fostering interactions between assay developers and diversity libraries in an effort to create both a sophisticated informatics system and an outreach to the community so that biologists with innovative assays find chemists with libraries of potential relevance to those assays; and funding studies to screen compound libraries. In addition, the Institute is working to establish Centers of Excellence for Drug Development – multidisciplinary and translational research teams – each of which will be organized around a mechanism of particular relevance to cancer prevention or therapy. The multidisciplinary research groups of chemists, biologists, pharmacologists, imagers, clinicians, and informatics experts within the Centers will collaborate to create the tools needed to clinically assess and validate the effects of drugs on molecular targets.

An important step in this research area involves providing the opportunity to use basic discoveries rapidly and efficiently toward the development and testing of new prevention and treatment agents. Often, promising hypotheses and candidate molecules are conceived within the academic community, yet limited resources restrict academic investigators or institutions from testing them in the clinic. Without pharmaceutical company interest in a new molecule, an investigator has little chance to negotiate the costly and specialized steps involved in the bulk synthesis, formulation, pharmacology, and toxicology needed to ready a drug for Phase 1 clinical trials. To eliminate these barriers, NCI is implementing two new programs to help academic institutions bridge the gap between discovery and clinical testing and ensure that the most promising agents are tested in an adequate and timely fashion. Rapid Access to Intervention Development (RAID) is designed to facilitate the translation to the clinic of novel, scientifically meritorious therapeutic interventions originating in the academic community. Rapid Access to Preventive Intervention Development (RAPID) is designed to provide assistance for the research and development of agents that may prevent, reverse, or delay carcinogenesis. Both programs give academic investigators access, on a competitive basis, to NCI's development resources for the pre-clinical development of preventive and therapeutic drugs and biologics.

Finally, to more efficiently convert recent scientific discoveries into effective interventions, NCI is working to restructure and increase the capacity of our national clinical trials program. By reconfiguring major aspects of the program, we hope to speed and smooth the path for entering promising agents into trials, to substantially increase the number of trials and the number of

patients who enroll in trials by easing the way for physicians to communicate with patients and enroll them in trials, and to fund the kind of laboratory studies that will help determine why particular drugs are effective in some patients but not in others. Such enhancements to the program will hasten the development of agents and alleviate the backlog of agents awaiting evaluation.

Tobacco and Tobacco-Related Cancers Research

A wealth of scientific studies have demonstrated that the use of tobacco – cigarettes, cigars, pipes, and smokeless products – increases a person's risk for a host of cancers (lung, mouth, pharynx, larynx, esophagus, pancreas, cervix, kidney, and bladder), heart disease, and a range of other health conditions. These studies have provided important information about the genetic and molecular factors that underlie a cell's transformation from normal to cancerous following exposure to carcinogens in tobacco. We still have far more to learn, however, about how and why elements in tobacco smoke target particular genes and how tobacco-induced cellular damage initiates and promotes cancer development. Such knowledge will help us identify precancerous lesions and markers that may predict tobacco-induced cancer and may provide important insights into why some people – perhaps because of their genetic constitution – are more vulnerable to tobacco's harmful effects. It also will inform prevention and detection strategies, and in particular, allow us to develop approaches that target vulnerable individuals.

Increasing evidence suggests that genes and their interaction with environmental factors also appear to influence smoking behavior and risk for addiction. In fact, major research breakthroughs recently provided important insights into the biological basis of tobacco use and nicotine addiction, including the role of genetic factors and ethnicity. Such discoveries are offering unique opportunities to study the links between biology and behavior and will help identify preexisting vulnerabilities to tobacco use. By determining how these vulnerabilities interact with sociocultural and psychological influences on tobacco use – and by improving our ability to quantitatively assess risks – we can develop more effective prevention and cessation approaches and tailor them to people most likely to benefit from them.

NCI continues to pursue a number of programs and initiatives in tobacco research to respond to the major threat that tobacco use poses to life and health. Activities in basic biological research include: prospective studies to identify genetic and biological factors that may increase or decrease susceptibility; innovative studies to determine the mechanisms by which tobacco use contributes to the development of non-aerodigestive cancers such as pancreatic, cervical, and bladder cancers; the development of a tobacco carcinogenesis models forum to link expertise of participants in the Mouse Models of Human Cancer Consortium to investigators with expertise in behavioral and other models of tobacco carcinogenesis; supplemental research grants to identify genes that increase the risk of nicotine addiction; and international collaborative studies to explore how environmental and other factors interact with genes to influence the likelihood and age of smoking initiation, intractability of addiction, and risk of tobacco-related disease.

Given tobacco's link to cancer, there is a critical need to develop strategies that prevent people from ever starting to smoke, help those who currently smoke to stop, and more effectively detect and treat tobacco-associated cancers. To meet this pressing need, NCI is pursuing a number of prevention initiatives, including initiating trans-NIH epidemiological studies to track familial,

environmental, and biological risk factors within the same individual over time to better understand the determinants and health consequences of tobacco use in children and adults. Recognizing that tobacco use and its health consequences are not evenly distributed across the population, NCI plans to develop a consortium of investigators and community members who will work to identify gaps and needs in research aimed at preventing tobacco use among high-risk groups and disseminating the best practices to communities. In the area of *smoking cessation*, the Institute is focusing on efforts to develop and evaluate new, powerful pharmacotherapies and drug combinations to help people stop smoking and remain tobacco-free. New behavioral techniques and technologies that amplify the effects of other treatments are also being explored. Finally, for those whose smoking history places them at increased risk for cancer, NCI is working to support studies to improve our ability to detect cancer in its earliest - and most treatable – stage, and to effectively treat cancer once it has developed. Central to NCI's early detection effort is the Early Detection Research Network (EDRN), a national scientific consortium of academic and industrial researchers. EDRN scientists are working to identify and validate markers that indicate tobacco exposure and tobacco-induced cellular events leading to cancer. NCI also hopes to support projects to develop and test preventive agents and therapies.

The multifaceted nature of tobacco research calls for effective collaborations among basic, clinical, and population scientists and across diverse fields of science and technology. To facilitate these efforts, NCI is expanding support for its Transdisciplinary Tobacco Use Research Centers. These Centers, which are jointly supported by NCI and the National Institute on Drug Abuse (NIDA), facilitate collaborations among researchers in areas ranging from molecular biology, genetics, neuroscience, and epidemiology to imaging, primary care, behavioral science, communication, health policy, economics, and marketing. These centers also serve as training grounds for the next generation of tobacco scientists.

Cancer Communications

Communication is central to effective, quality cancer care, from prevention to survivorship and end-of-life issues. Communication empowers people; it raises awareness of health problems and recommended actions; and it provides people the information they need to make informed cancer-related decisions. Effective communications can move people to engage in behaviors that will improve their health, such as stopping smoking or undergoing screening for certain types of cancer. The Department of Health and Human Services' Science Panel on Interactive Communications and Health has concluded that few other health-related interventions have the potential of interactive health communications to simultaneously improve health outcomes, decrease health care costs, and enhance consumer satisfaction.

Changes in the role and accessibility of information are altering health care practices, patient-physician relationships, and the way consumers and patients acquire and use information. While physicians once were the main source of health information, new communications technologies now provide new opportunities for creating, distributing, and acquiring health information from the World Wide Web, individually tailored print and multimedia materials, interactive computer games, interactive kiosks, and wireless pagers. This expanding and evolving world of communication demands a cohesive, coordinated initiative, and provides NCI with an extraordinary opportunity for investment and impact.

To pursue the opportunities is this new area, NCI will enhance its communication research capabilities and their application through a number of avenues. One is to establish new data collection and analysis strategies to obtain data at regular intervals for cancer communications planning, research, evaluation, and marketing. Another is to create Cancer Communications Centers of Excellence to provide interdisciplinary units for communications research, including cancer risk communication, new tool and product development, and practical information dissemination enhancement methods. NCI is developing an integrated cancer knowledge management strategy, including an adapted and redesigned Cancer Information Service (CIS) that offers a menu of communication choices designed to meet and respond to people's diverse information needs. We have begun redesigning the Physician's Data Query (PDQ) based on usability testing to make information more accessible and easier for all users to navigate. The new PDQ Universal Database stores any type of cancer-related information – images, sound, movies, text – and delivers it in a variety of forms.

NCI is also developing new products to facilitate cancer communications to diverse audiences. We are training the health communications scientists, researchers, and practitioners needed to achieve our scientific and health communications objectives. Lastly, the Institute will identify, create, and nurture use of the newest and most promising communication technologies by partnering with the creators of leading-edge technologies to modify existing products and develop new ones that meet the cancer information needs of diverse audiences.

Understanding the Burden of Cancer

Identifying and tracking cancer trends and monitoring the factors that influence these changes is a crucial underpinning of our efforts to prevent and control cancer. Discovering national trends in cancer helps us identify those populations most at risk for specific cancers, informs treatment efforts, and can help to better define survivorship issues. For more than twenty years, NCI's Surveillance, Epidemiology, and End Results (SEER) cancer registry program has monitored the Nation's cancer burden and been a world model for tracking population trends in cancer incidence, survival, morbidity and mortality. To more fully assess our Nation's cancer burden, NCI has several initiatives planned and underway to enhance SEER to improve our ability to describe the cancer burden across a broader spectrum of the population, to expand data collection to include information on screening practices, treatment options and patterns of care, and to develop methodological tools to expand the reach of our surveillance efforts. NCI also is leading a Department of Health and Human Services (DHHS)-wide initiative to ensure that all Americans receive the highest quality of cancer care, spanning a continuum that encompasses prevention, diagnosis, treatment, rehabilitation, survivorship, and end-of-life care. These initiatives are described below.

Emerging Trends in Cancer

Through cancer statistics and studies we know that not all populations are affected equally by cancer. Some population groups develop cancer more often and have poorer survival rates than others. These special populations include ethnic minorities, geographically isolated and other medically underserved populations, the elderly, women, people of diverse cultures and lifestyles, and people with lower income, education, and literacy levels. NCI plans to expand the SEER program to collect data on a wider range of population subgroups and on socioeconomic and other factors that underlie cancer trends. As many as four new state registries will be added to

SEER, and up to ten additional states will receive supplementary funding to upgrade their existing registries to meet SEER standards. This expansion will be achieved in partnership with the Centers for Disease Control and Prevention, and will capture data on a broader spectrum of Native American and Hispanic population subgroups, rural African Americans and whites, and others. NCI also has several initiatives planned to support and expand SEER special studies such as the Prostate Cancer Outcomes and the Patterns of Care studies.

NCI also is responding to the growing recognition of the importance of additional measures and methods that go beyond the core indices of incidence, survival, and mortality used to characterize the cancer burden. Several initiatives are underway to expand data collection to include more information on patterns of care, outcome measures, and geographical distribution of cancer cases. Methodological tools that will improve the precision and expand the reach of our surveillance tools are needed. These tools include geographic information systems (GISs) that allow data linkage of geographic location, new approaches to modeling, and more refined cancer maps for assembling, analyzing, and disseminating cancer surveillance data. GISs are powerful computer systems that can store, manipulate, analyze, and display the spatial (geographic location) relationships between dissimilar data types. They provide a tool to study the potential relationships for example between location of breast cancer cases and sources of air or water pollution. NCI recently awarded a contract to develop and implement a prototype GIS for breast cancer as part of the Long Island Breast Cancer Project. In addition, there is a critical need to develop methods in statistical surveillance analysis. NCI is developing a new program called the Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET will include a consortium of centers that support modeling research of population-based trends in risk factors, screening, and treatment related to cancer outcomes; help design, interpret, and extrapolate screening and prevention studies; and evaluate cost and health effects of specific interventions.

Quality of Cancer Care

American Cancer Society estimates indicate that more than eight million Americans were treated for cancer in 1999, with 1.2 million having newly diagnosed cases.[7] The toll in human pain and suffering will be keenly felt by the millions of individuals and families who bear the burden daily. In the forefront of developments in the basic, clinical, and population sciences to uncover the underlying causes of cancer and to translate this knowledge into effective interventions, NCI now proposes an expanded research strategy for improving the quality of cancer care. The overall objective of this new NCI initiative is to design and foster the development of research programs, projects, and studies that enhance the state of the science for defining, monitoring, and enhancing the quality of cancer care. This initiative will be carried out in conjunction with the Secretary's Quality Improvement Initiative. NCI will work closely with a number of other Federal agencies as well as with an array of private sector organizations.

Critical elements of our quality of care research agenda will include the identification of valid, reliable, and feasible quality-of-care outcome measures that are patient-centered, acceptable to providers and payers, and span the continuum of care. Monitoring whether the solid evidence gleaned from clinical trials and good observational studies about what constitutes appropriate quality care has been translated successfully into community practice will also be critical. NCI

[7] American Cancer Society, Surveillance Research: *Cancer Facts & Figures 1999,* p. 1, 99-300M-No. 5008.99.

plans to work with the scientific community to ensure that the randomized trials that NCI sponsors become more attentive to a range of scientific, organizational, and outcome measurement issues that ultimately bear upon quality. Finally, this research also will focus on how to improve the quality of communications across the cancer spectrum, especially among patients, providers, and research communities. An enhanced surveillance system, the restructuring of the clinical trials program, and communications initiatives, including the creation of Communications Centers of Excellence, are some examples of initiatives and projects underway or planned that will begin to provide needed information on quality of cancer care.

OTHER AREAS OF INTEREST

Health Disparities
NCI is continuing to focus attention on better understanding issues related to differences in the incidence, prevalence, mortality, and burden of cancer that exist among specific population groups in the United States. We have reported above on several cancer "Science Advances" in this area and highlighted the significance of disparity issues in the earlier discussion of "Emerging Trends in Cancer." Some other activities at NCI that also address disparity issues are described below.

Special Populations Networks for Cancer Prevention and Control
NCI recently launched the Special Populations Networks for Cancer Awareness Research and Training, for which $30 million has been earmarked over five years. The funds will be used to support a diverse group of research projects aimed at improving cancer prevention and control in minority and underserved communities. Principal goals of the new Networks will be to develop and maintain partnerships between scientific researchers and community leaders in minority and underserved populations, develop and test community cancer awareness activities, support minority enrollment in clinical trials, and encourage minority scientists to participate in research.

Outreach and Education for Minority and Underserved Populations
NCI recently organized and expanded special populations biomedical training opportunities under the Continuing Umbrella of Research Experiences (CURE) initiative to attract, develop, and support researchers and cancer care givers from minority and underserved populations. CURE reaches minority students as young as high school age; develops undergraduate, graduate, and postdoctoral scientists; and supports young minority investigators as they establish their research careers. CURE also provides training support for individuals with disabilities and for scientists re-entering an active research career after taking time off for child care or other family responsibilities. NCI is also working to establish long-term partnerships between NCI Cancer Centers and minority-serving institutions to enhance the centers' approaches to outreach and education and participating institutions' approaches to conducting cancer research and to training future cancer scientists.

Special Populations Working Group
NCI has assembled a Special Populations Working Group to enhance its priority- setting and information dissemination processes and strengthen communication with the many groups, organizations, and institutions involved in special populations issues. Group members are drawn from a variety of medical and non-medical disciplines, individuals knowledgeable about the

cancer experience, and diverse communities. The Group raises and articulates special populations concerns and issues, makes recommendations for addressing special populations issues at the NCI, suggests NCI-community partnerships to reach common goals, and provides an ongoing communication channel with diverse minority and other special populations communities.

Genes and the Environment

Fueled by conceptual and technical breakthroughs, the often breathtaking pace of scientific discovery has generated optimism among researchers that new avenues will be found to detect, treat, and prevent cancer. This sense of excitement is great at the interface of the fields of genetics and epidemiology where information revealed in epidemiologic studies can be married with molecular technologies to help us understand the genetic and environmental factors and their interactions that contribute to cancer. Described below are several NCI initiatives designed to harness this critical information.

Conducting Large-scale Population Studies

Through studies of rare cancer-prone families we have opened a unique window into the basic mechanisms of cancer by identifying altered forms of normal genes involved in key pathways controlling fundamental cell processes. It is now clear that these same pathways contribute to the development and progression of more common, non-hereditary forms of cancer. The opportunity now exists to determine how variations in these genes that contribute to familial cancers combine with environmental and other factors to induce cancer in the general population. To uncover gene-environment interactions in the general population we will conduct prospective, population-based studies involving a total of one million participants and develop the infrastructure for case-control studies initially involving 20,000 participants with particular attention given to tumors of with rising incidence and mortality rates, racial and ethnic disparities, and unusual geographic patterns. We are also developing repository, laboratory, and informatics infrastructures for conducting large gene-environment studies.

Assessing Environmental Exposures

The ability to measure and evaluate environmental exposures and their effects on genes will be crucial to our understanding of cancer and its causes. But as technology for genetic assays continues to advance, the key source of error in assessing gene-environment interactions will be in the estimation of environmental exposures. We must develop investigational strategies and technologies that will enable us to deal with problems inherent in assessing exposures including multiple and diverse exposures, the variety of techniques for measurement, and the different media used for testing (e.g., tissues, body fluids, environmental samples, archival records).

Promising avenues of research include computer-assisted interviewing techniques, biologic dosimeters in normal tissues and in tumors, practical environmental monitors, and novel analytical approaches for synthesizing environmental data. In addition, further work is needed to develop non-invasive methods for collecting DNA for molecular studies, and techniques to maximize the use of small quantities of material for exposure and genetic studies. NCI is creating more effective means of assessing environmental exposures by providing supplemental funding for investigators involved in population studies to conduct focused methodological work in exposure assessment; developing non-invasive methods for collecting DNA and techniques to

maximize the use of small quantities of genetic material; using the Geographic Information Systems working group to identify priority areas for research and to stimulate and coordinate research in this area; issuing a Program Announcement with NIAID for developing and applying technologies for screening biologic samples to identify infectious agents relevant to cancer.

Discovering Gene Variations
Identifying cancer-related genes and their variants is critical to increasing our understanding of what causes cancer, how it develops, and how best to prevent or treat cancers. The Genetic Annotation Initiative (GAI), a component of NCI's Cancer Genome Anatomy Project (CGAP), is our primary program for uncovering variants of cancer genes. The goal of CGAP is to determine the complete profile of active genes in normal, precancerous, and cancer cells, with the aim of making it possible to recognize all major steps of tumor development. The GAI has identified and made available via the Web information on over 10,000 variations of CGAP-discovered genes. In addition, the GAI's Technology Partners Initiative has been established to expand the array of tools available for genetic analysis. NCI is also continuing to pursue the development of long-range, high-impact technologies through its Unconventional Innovation Program (UIP). NCI is expanding CGAP programs to identify all cancer-relevant genes and common variants; extending GAI's efforts to define key molecular pathways by increasing CGAP's capacity to assess gene expression profiles and by establishing working groups to develop and curate information on cancer genes and their related pathways; and accelerating new technology development and application by expanding the UIP and GAI Technology Partners initiatives.

In addition to these initiatives, NCI will continue to: develop new experimental models that parallel human cancer-related genes, pathways, and processes; conduct studies of high-risk families to identify and characterize cancer-predisposing genes; develop risk assessment models that incorporate genetic and environmental information; and conduct clinical studies to address the clinical, behavioral, and societal issues associated with cancer susceptibility.

Innovations in Imaging Technology
Over the past quarter century, refinements in imaging technology have greatly improved our ability to detect, diagnose, and predict the course of cancer. Imaging tests such as X-ray mammography, computed tomography (CT), and ultrasound provide clearer and more detailed pictures of organs and tissues than were possible previously, thus improving detection and diagnosis of cancerous tumors. The new frontier in imaging technology lies in the development and application of functional imaging tools and agents that allow us to visualize physiological, cellular, or molecular processes in living tissue. Significant advances have occurred in functional imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and optical imaging. Further advances are possible in oncology by merging the developments in imaging sciences with the new discoveries in cancer-related genes and proteins. As we gain a better understanding of the fundamental nature of cancer, cellular and molecular imaging will be a key tool in translating this knowledge into better ways of diagnosing, treating, and preventing cancer.

Biomedical imaging is technology intensive, and discovery, development, and advancements in imaging modalities require support of projects at all levels, including development of structural and functional imaging tools, application of the technology in a clinical setting, and development

of measures of effectiveness. NCI has made a substantial commitment over the past several years to supporting research and technology development aimed at advancing imaging to more fully exploit its promise in cancer research and care. NCI has launched several exciting initiatives including the creation of *In vivo* Cellular and Molecular Imaging Centers (ICMICs) that facilitate interaction among scientists from a variety of multidisciplinary fields to conduct research on cellular and molecular imaging, the development and application of imaging therapeutic studies, an initiative to support research projects that address the development and application of labeled therapeutic agents as compounds for imaging studies, and the Small Animal Imaging Resource Program, a program to support the development and application of a variety of imaging modalities focusing on functional, quantitative methods applicable in humans.

To evaluate innovative emerging methods of diagnostic imaging and image-guided therapy, NCI recently provided funding to support the American College of Radiology Imaging Network, an initiative that brings together imaging experts from around the nation to perform a broad spectrum of multi-institutional clinical trials on diagnostic imaging tools related to cancer. In addition, NCI issued an announcement seeking applications to advance the state of art in digital mammography displays and workstations. Digital mammography is considered one of the most promising technologies for use in large-scale screening programs to improve early breast cancer detection. NCI has also launched an initiative to support the development of non-invasive imaging technologies for the localization, biopsy, and minimally invasive treatment of prostate cancer. Furthermore, via the Phased Innovation Award, NCI is soliciting applications for innovative technologies for molecular analysis of cancer. Technologies under consideration include those that will support molecular analysis *in vivo*, by imaging or other methods, in the cancer detection and development process, as well as in clinical application.

In the coming year, NCI has a number of new initiatives planned to enhance imaging technology in cancer research. These include initiatives to support Cooperative Groups in the development of an image database for breast, lung, and colon cancer, using retrospective cases and images formed by digital X-ray or spiral CT; the development of ultrasound interface for use by imaging researchers; supplements to the mouse models consortium to include imaging expertise; and the creation of Optical Imaging Centers. In addition, NCI has initiated a major effort to enhance its interactions and collaborations with industry and academia, essential components in the successful development of new and improved imaging technologies. In September 1999, NCI convened the first NCI-Industry Forum and Workshop on Biomedical Imaging in Oncology. This Forum brought together Federal agencies, academia, and industry creating a needed synergy to respond to the rapid pace of innovation, discovery, and new developments in basic science, imaging technology, and cancer research in general. Plans are underway to foster this synergy through the formation of working groups of Forum participants and future Forum meetings over the next year.

Centers of Research Excellence

The rapid pace of scientific and technological discoveries has created enormous opportunities in the fight against cancer. For example, the revolution of molecular biology and genetics, along with the emergence of powerful technologies, are providing us with critical insights into how we can prevent, detect, diagnose, and treat cancer. The challenge for NCI is to establish the mechanisms that will allow the scientific community to apply these discoveries and emerging

technologies to the field of cancer research. We need mechanisms that will promote and reward innovative thinking, the cross-fertilization of ideas across scientific disciplines, and enhanced collaborations among government, academia, and industry. We need to create new kinds of functional links – not only among basic, clinical, and population scientists, but also across very diverse fields of science and technology. We need productive interfaces among mathematicians, biologists, computer scientists, epidemiologists, imaging scientists, chemists, physicists, and clinicians. Similarly, as scientific and technological development provides us with new tools to intervene at many points along the entire trajectory of malignancy, the actual testing of these new interventions – whether for prevention, detection, diagnosis, or treatment – will require access to many different kinds of resources, such as patients, at-risk populations, tissue banks, new technologies, and state-of-the art informatics.

To improve access to these resources and create the multidisciplinary links, NCI proposes to expand its program for Centers of Research Excellence to develop a variety of new research networks and consortia. Centers of Research Excellence are multidisciplinary and translational research teams focused on specific disease, modality, biologic process, or scientific area of particular significance. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities or specific challenges. NCI's Specialized Programs of Research Excellence (SPORE) is one highly successful example of this approach. Each SPORE group focuses on a specific cancer site. Their goal is translational: they aim to move discoveries and observations back and forth among laboratory, clinic, and population settings. Recent findings from SPORE include the identification of several tumor suppressor gene mutations that lead to pancreatic cancer and the first human gene therapy approaches for advanced prostate cancer. NCI is supporting SPOREs in cancers of the breast, prostate, lung, gastrointestinal tract, and ovary.

Additional examples of the Centers of Research Excellence concept that have recently been established or will shortly be established include the Transdisciplinary Tobacco Use Research Centers and the *In vivo* Cellular and Molecular Imaging Centers. In FY 2001, NCI plans to expand the program even further by creating Cancer Communications Centers of Excellence to provide interdisciplinary units for communications research; Centers for Population Health to integrate epidemiologic, behavioral, and surveillance research; Centers of Excellence for Drug Development organized around a mechanism of particular relevance to cancer prevention or therapy, (e.g., angiogenesis, cell-cycle control, immunotherapy, DNA-damage repair, cell signaling, differentiation, metastasis, or apoptosis); and Optical Imaging Centers of Excellence that will provide an organizational structure to facilitate the integration of basic and clinical sciences focused on the translation and assessment of optical technologies in the clinic.

New Technologies in Cancer Research

Within the human body, tissues are complicated three-dimensional structures composed of multiple populations of cells that have developed to perform a particular job in the body. Studies have demonstrated that cells in this natural tissue environment may express quite different proteins than cultured cells or even cells transplanted into animals. Such knowledge has generated a need for technology that can identify and directly measure the level of a specific protein, or protein pathway, in actual tissue cell populations. In response to this need, NCI and the FDA have jointly launched a new program, known as the Tissue Proteomics Initiative, aimed

at developing and applying new approaches to analyze the state of proteins and pathways in human tissue cells undergoing disease progression, manifesting a toxic response to treatment, or undergoing a response to an experimental treatment.

A technique that has proven to be vital to this area of research is laser capture microdissection (LCM). This simple tool bridges the studies of basic molecular genetics and human genetics, enabling scientists to easily extract cells selectively from heterogeneous tissue and isolate and study patterns of gene and protein expression in cells from an array of human diseases including cancer, Alzheimer's Disease, and Multiple Sclerosis. LCM, coupled with other techniques, is offering exciting new opportunities in the proteomics field to study normal, diseased, or genetically modified tissue. For example, NCI scientists recently used a sensitive quantitative chemiluminescent immunoassay to measure the number of prostate specific antigen (PSA) molecules per cell in cells extracted by LCM from a heterogeneous prostate tissue sample. This approach verified that PSA protein content varies among the different cell types captured in a heterogeneous prostate tissue sample (normal cells, prostate intraepithelial neoplastic cells, and invasive carcinoma cells), demonstrating for the first time that LCM and the chemiluminescent immunoassay can be used to quantify protein in pure microscopic populations of tissue cells.

The complicated, changing pattern of protein expression contains important information about the disease process taking places in the cells of human tissues. Until recently, however, scientists have been unable to use this information because the tools to rapidly analyze changes in protein expression in defined microscopic cell populations have not existed. Now, NCI and FDA investigators have developed a tool using biochip technology, known as Surface Enhanced Laser Desorbtion Ionization (SELDI), to generate sensitive, rapid, and reproducible protein biomarker profiles of patient-matched normal, premalignant, malignant, and metastatic microdissected cells from human esophageal, prostate, colon, and liver tissue sections. Tissue cell proteins that bind to a special capture bait on the surface of a metal chip – similar to a computer chip – are detected with a laser beam. The proteins then are characterized by their weight; using this information, scientists generate a profile – or a fingerprint – of the captured proteins in a readout similar to a bar code. These protein profiles can be obtained from as few as 25 cells in less than five minutes. Biomarker pattern profiles reveal changes in protein expression as cells transition from normal, to premalignant, to invasive cancer. Consistent protein changes were identified in studies using microdissected cells from patient-matched tumor and normal prostate and esophageal epithelium from a patient study set. This promising new tool may be of great use in the discovery of disease-related proteins, assessment of new therapies, and monitoring of possible toxic effects of new treatments.

Complementary and Alternative Medicine

NCI is steadily building an environment that fosters the convergence of ideas from traditional and alternative approaches to the goal of eradicating cancer. We have established the NCI Office of Cancer Complementary and Alternative Medicine (OCCAM) to coordinate our broad range of activities in this area, including strengthening our relationship with the NIH National Center for Complementary and Alternative Medicine (NCCAM), the careful evaluation of CAM therapies, and the development of accurate CAM information for the public. By employing rigorous methodologies to studies in complementary and alternative medicine, NCI continues to support many high-quality, CAM-related research projects, such as evaluating green tea as a cancer

prevention agent; evaluating a novel nutritional therapy; examining the therapeutic value of vitamins and minerals in cancer treatment and prevention; studying stress and pain management to enhance the quality of life for cancer patients; and examining the effect of natural inhibitors of carcinogenesis. In addition, we are supporting NCCAM in establishing a center for CAM research that would provide the resources necessary for the rigorous scientific study of CAM approaches.

NCI is also collaborating with NCCAM on the establishment of a Cancer Advisory Panel regarding CAM (CAP-CAM). The CAP-CAM will meet two to three times a year and draw its 15 members from a broad range of experts from the conventional and CAM cancer research community. This group will review and evaluate summaries of evidence for CAM cancer claims submitted by practitioners, make recommendations regarding follow-up of evaluations, and observe and provide advice about studies supported by NCCAM and NCI and communication of results. There have been two submissions from the homeopathy community for review.

The public availability of accurate, up-to-date information about CAM therapies is an important component of NCI's cancer information and dissemination efforts. Detailed CAM summaries are being prepared for therapies identified by our Cancer Information Service and the NCCAM Clearinghouse as being of public interest. Development of the summaries will follow the same model as those for conventional therapies and include specific trial results and references to the published literature. They will be reviewed by the appropriate Physicians Data Query (PDQ) Editorial Board and will be sent to experts in the CAM community for review before they are made available on NCI's web site.

NCI established a lecture in CAM as part of the medical grand rounds series in our Division of Clinical Sciences; it is open to all members of the NIH community interested in CAM. NCI has also initiated a Cancer Complementary and Alternative Medicine Research Interest Group.

Detection, Diagnosis and Prognosis

At the cusp of the 21st century, the development of molecular-based technologies is revealing to us the structural changes in cells that are the first harbingers of cancer. These new technologies enable us to identify features of individual cells in ways impossible just twenty years ago. For example, all cell types have unique, identifiable signatures; these are specific characteristics, such as the genes that code for proteins and other cellular products. Our new technologies enable us to read and understand those signatures: during the transformation of a normal cell to a cancer cell, the signature changes, and that change signals the presence of cancer.

We have also learned that cells surrounding the incipient tumor may also undergo changes to indicate that cancer is present. Reading the signatures of these easily accessed cells eventually will lead to the development of simple, non-invasive tests to find cancers located deep within the body. For example, with additional research, we can expect the diagnostic tests of tomorrow to include those that find tobacco-induced molecular changes in the mouth that will predict the risk of developing lung cancer, and simple urinanalyses that will detect cancers of the urinary tract by identifying cancer cells that are shed in the urine. We can already use changes in molecular signatures to help us identify infectious and environmental agents that may influence tumor development or progression. Such "molecular fingerprinting" will allow us to differentiate

among tumors at the molecular level, enabling us to devise treatments targeted at cellular subtypes of different cancers and detect and diagnose cancers at the earliest stages.

The past several years have seen an explosion of discovery in this area. NCI's new and ongoing initiatives include the Human Tumor Genome Index (TGI). The primary goal of the TGI is to identify the genes expressed during the development of human tumors. Gene identification is accomplished through the construction of cDNA libraries, or representations of the expressed genes in normal and cancerous tissue. To date, 130 cDNA libraries have been prepared by CGAP and more than half a million partial cDNA sequences have been generated. Data from the CGAP have been used to discover more than 24,100 human genes.

In addition, NCI has dedicated over seven million dollars to creating a multi-institutional Early Detection Research Network to develop sensitive and specific tests for the earlier detection of cancer. The Network, which will have three components – Biomarkers Developmental Laboratories, Biomarkers Validation Laboratories, and Clinical/Epidemiologic Centers – will link centers of expertise in tumor biology, diagnostic technologies, and clinical trials methodology in academia and industry to develop high-throughput assays suitable for clinical application. To expedite the discovery and development of more sensitive and specific markers for early disease, NCI will also establish links between activities of the Network and programs in academia and industry that are developing libraries of secreted proteins in mammalian cells. The NCI Director issued his Challenge for Molecular Diagnostics to the research community to revolutionize the classification of human tumors. Traditionally, the classification of tumors has been based on morphology, or the tumor's structure. But morphological classification cannot accurately predict biological behavior, prognosis, and response to treatment. We anticipate that the research community will rise to the challenge and discover new ways to combine technological advances in molecular detection with rapidly advancing knowledge of tumor biology to provide a more clinically predictive and useful system of tumor classification.

Animal models that truly mimic the development and progression of human cancer and its response to intervention would profoundly affect our ability to understand the process of malignant transformation, and could improve our ability to evaluate a range of biomarkers. To meet the need for animal models in a variety of settings, NCI is soliciting applications to establish a consortium to develop and validate mouse models for human cancer. NCI has also issued a call for grant supplements from investigators interested in developing mouse models of human cancer as an extension of the approved content of their grant. Additional supplements for model systems other than the mouse will also be considered.

INNOVATIONS IN MANAGEMENT AND ADMINISTRATION

Around the globe, cancer researchers are benefitting from advances in computing and telecommunications that, coupled with the explosive growth of the World Wide Web, help make unprecedented research opportunities possible. These advances in technology allow for collaboration and the generation of stupendous amounts of information – the raw material from which knowledge is created. But vast amounts of information that already exist often go unused because of users' inability to access and organize information from diverse sources. Therefore, we must ask ourselves, how do we best collect, manage, and share this information?

The answer to this question lies in information management – in designing a framework to help capture, analyze, apply, and reuse information to make possible faster, smarter, and better applications. This framework will serve as a tool to create a critical interface among the research communities – basic, translational, clinical, and population-based – that participate in the research discovery process, and most importantly, in the generation of knowledge.

Computerized Personnel System
NCI is using two state of the art, web-based human resources software programs that substantially streamline human resources work. One automates the processes of writing and classifying position descriptions, and developing recruitment and staffing documentation for supervisors. The other enables supervisors to select specific employee relations events in the database to produce a variety of documents (e.g., legal standards, situation-specific risk and liability assessment, and relevant correspondence) to effectively deal with a situation.

User Services Group
NCI began an outreach program to increase awareness and understanding of centrally provided computer services, to streamline access to the services, to enhance computing skills through training and other means, and to identify user requirements to the service providers.

Storage of Research Data
As scientific research becomes increasingly dependent on information technology, data storage needs grow at a rapid pace. These data, comprising images produced by confocal and other forms of microscopy and significant amounts of genomic information, are available to PCs, Macs and Unix machines. By the end of FY2000, over 1600 gigabytes will be dedicated to storage.

Chip Technology Brings Savings and Sharing
The NIH scientific community uses a technically complex, highly expensive research tool, known as the "gene chip," viewed as critical to continued participation in the ongoing genetic medicine revolution. NCI negotiated a significantly reduced cost for the gene chip technology and associated training that balanced the complexities of intellectual property rights with cost without setting a precedent that could affect future agreements. Other institutes across NIH have used this contract to purchase this important new scientific tool at substantial savings to the government. The academic research community may also purchase the technology on comparable terms.

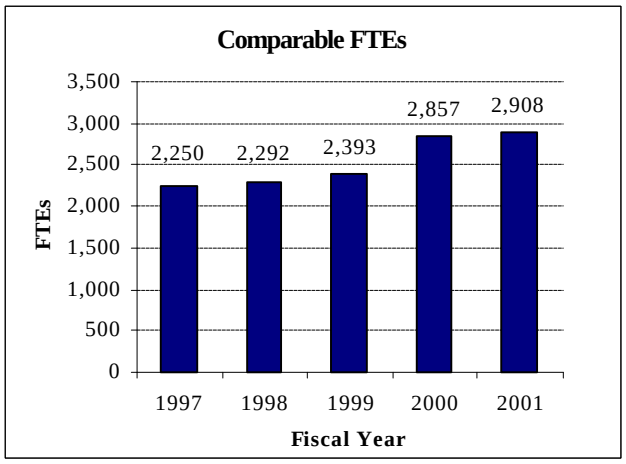
Diversity Programs
NCI has consolidated and redefined its Equal Employment Opportunity Office, Quality of Worklife, and recruitment and retention services to create a comprehensive and proactive Office of Diversity and Employment Programs (ODEP). ODEP initiatives include development of on-line diversity training for NCI employees and communication of diversity awareness through various mechanisms including e-mail, desk-to-desk and newsletter articles, and presentations. NCI also established a Recruitment Office for administrative and scientific employees at all grades and classifications. The Recruitment Officer will develop a database of mainstream and minority recruitment sources; develop recruitment materials; and develop a master calendar of opportunities for recruitment in various academic, professional and minority communities.

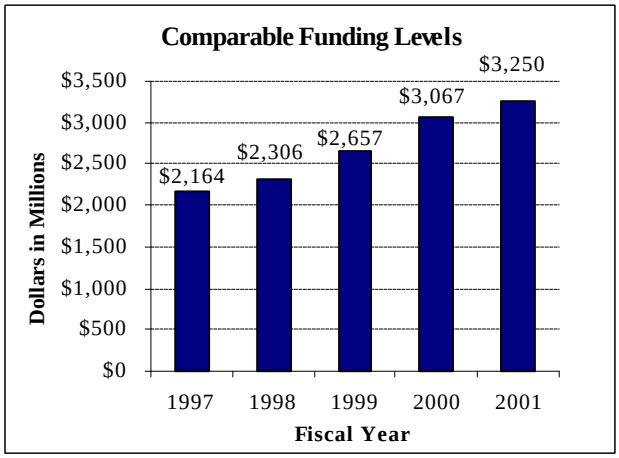
BUDGET POLICY

The Fiscal Year 2001 budget request for the NCI is $3,249,730,000 excluding AIDS, an increase of $182,537,000 and 6.0 percent over the FY 2000 level. Included in this total is $71,000,000 for the following NIH Areas of Special Emphasis:

New Approaches to Pathogenesis	$22,000,000
New Preventive Strategies Against Disease	10,000,000
New Avenues for the Development of Therapeutics	13,500,000
Genetic Medicine	10,000,000
Bioengineering, Computers and Advanced Instrumentation	10,500,000
Health Disparities	5,000,000
Total	**71,000,000**

A five year history of FTEs and Funding Levels for NCI are shown in the graphs below:





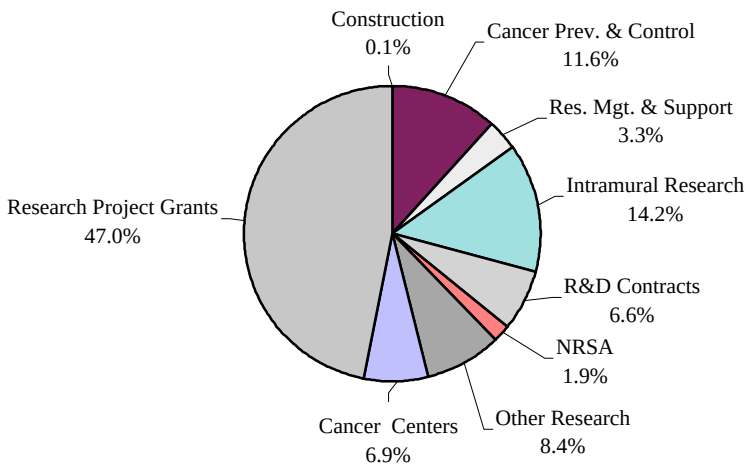
One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. To control the growth of continuing commitments and support planned new and expanded initiatives, the Fiscal Year 2001 request provides average cost increases of 2 percent over Fiscal Year 2000 for competing RPGs. Noncompeting RPGs will receive increases of 2 percent on average for recurring costs. This strategy will ensure that NIH can maintain a healthy number of new awards, especially for first time researchers.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2001 request, NCI will support 1,675 pre- and postdoctoral trainees in full-time training positions. Stipends will increase by 2.2 percent over Fiscal Year 2000 levels.

The Fiscal Year 2001 request includes funding for 84 research centers, 890 other research grants, including 86 new clinical career awards, and 107 R&D contracts. The mechanism distribution by dollars and by percent change are displayed below:

FY 2001 Budget Mechanism

$3,249,730

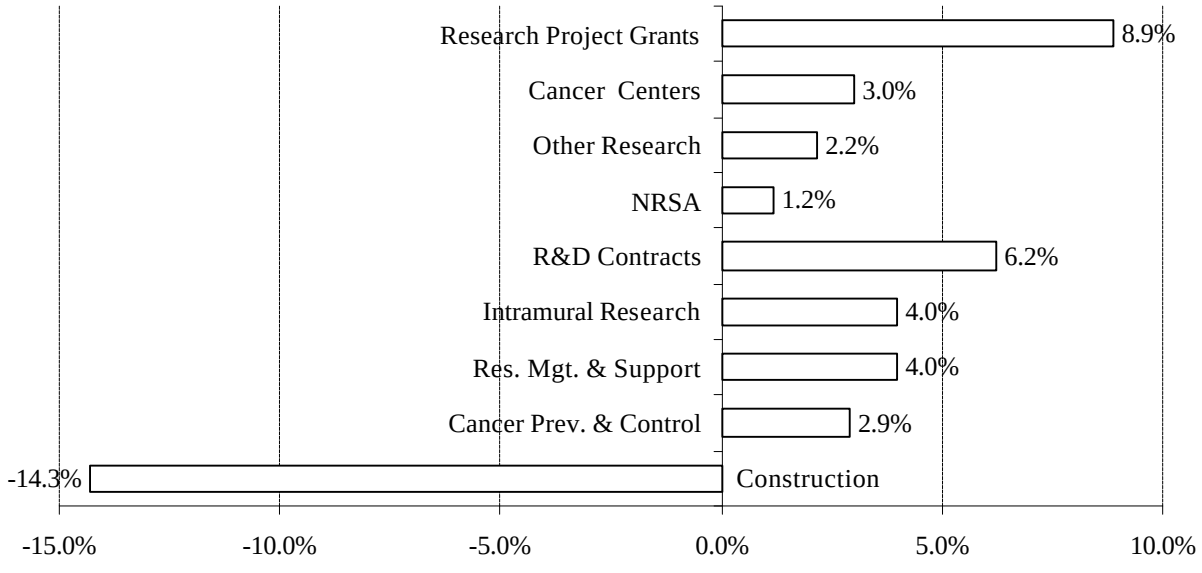


(Dollars in Thousands)

Research Project Grants (RPGs).....	$1,527,427	Research & Development Contracts.....	$215,832
Cancer Centers.....	223,064	Intramural Research.....	461,802
Other Research.....	274,313	Research Management & Support.....	108,430
[Clinical Cooperative Groups].....	[153,718]	Cancer Prevention & Control.....	375,367
National Research Service Awards.....	60,495	Construction.....	3,000

FY 2001 Estimate

Percent Change from FY 2000 by Mechanism



NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Budget Mechanism

MECHANISM	FY 1999 Actual		FY 2000 Estimate		FY 2001 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	2,555	$853,935,000	2,930	$948,786,000	3,182	$1,068,062,000
Administrative supplements	294	21,461,000	308	25,076,000	308	24,876,000
Competing:						
Renewal	289	109,704,000	325	136,209,000	325	137,571,000
New	862	208,527,000	873	223,955,000	861	226,195,000
Supplements	6	2,353,000	2	462,000	2	467,000
Subtotal, competing	1,157	320,584,000	1,200	360,626,000	1,188	364,233,000
Subtotal, RPGs	3,712	1,195,980,000	4,130	1,334,488,000	4,370	1,457,171,000
SBIR/STTR	291	56,863,000	329	68,098,000	329	70,257,000
Subtotal, RPGs	4,003	1,252,843,000	4,459	1,402,586,000	4,699	1,527,428,000
Research Centers						
Specialized/comprehensive	77	186,493,000	84	216,566,000	84	223,064,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Inst	0	0	0	0	0	0
Subtotal, Centers	77	186,493,000	84	216,566,000	84	223,064,000
Other Research						
Research careers	309	28,631,000	451	43,915,000	451	44,500,000
Cancer education	94	16,624,000	118	21,292,000	118	21,818,000
Cooperative clinical research	155	119,459,000	165	149,988,000	165	153,718,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	3,018,000	0	4,023,000	0	4,023,000
Other	99	28,831,000	156	49,225,000	156	50,253,000
Subtotal, Other Research	657	196,563,000	890	268,443,000	890	274,312,000
Total Research Grants	4,737	1,635,899,000	5,433	1,887,595,000	5,673	2,024,804,000
Training	FTTPs		FTTPs		FTTPs	
Individual awards	190	6,478,000	190	7,140,000	190	7,242,000
Institutional awards	1,485	49,034,000	1,485	52,641,000	1,485	53,253,000
Total, Training	1,675	55,512,000	1,675	59,781,000	1,675	60,495,000
Research & development contracts	110	177,942,000	107	203,211,000	107	215,832,000
(SBIR/STTR)	5	1,269,000	5	1,307,000	5	1,307,000
	FTEs		FTEs		FTEs	
Intramural research	1,440	384,172,000	1,847	444,056,000	1,898	461,802,000
Research management and support	695	94,050,000	735	104,262,000	735	108,430,000
Cancer prevention & control	258	306,342,000	275	364,788,000	275	375,367,000
Construction		3,000,000		3,500,000		3,000,000
Total, NCI	2,393	2,656,917,000	2,857	3,067,193,000	2,908	3,249,730,000
(Clinical Trials)		(485,834,000)		(574,735,000)		(626,830,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 1999 Actual		FY 2000 Estimate		FY 2001 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:								
Cancer causation	707	$663,025	847	$722,138	863	$775,088	16	$52,950
Detection and diagnosis rsrch	129	195,987	154	226,158	157	242,294	3	16,136
Treatment research	792	736,665	945	866,249	963	919,802	18	53,553
Cancer biology	420	444,157	503	520,064	512	560,652	9	40,588
Subtotal, research	2,048	2,039,834	2,449	2,334,609	2,495	2,497,836	46	163,227
Resource development:								
Cancer centers support	17	188,236	19	218,530	19	225,107	0	6,577
Research manpower development	28	105,457	30	130,212	30	132,246	0	2,034
Construction	2	3,142	2	3,669	2	3,175	0	(494)
Subtotal, resource development	47	296,835	51	352,411	51	360,528	0	8,117
Cancer prevention and control	298	320,248	357	380,173	362	391,366	5	11,193
Total obligations	2,393	2,656,910	2,857	3,067,193	2,908	3,249,730	51	182,537
Unobligated balance lapsing		7		---		---		---
Total, Budget Authority	2,393	2,656,917	2,857	3,067,193	2,908	3,249,730	51	182,537

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

2000 Estimated budget authority				$3,067,193,000
2001 Estimated budget authority				3,249,730,000
Net change				182,537,000
	2000 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$170,443,000		$3,119,000
b. Annualization of January 2000 pay increase		170,443,000		2,088,000
c. January 2001 pay increase		170,443,000		4,730,000
d. One day less pay		170,443,000		(691,000)
e. Payment for centrally furnished services		82,698,000		3,473,000
f. Increased cost of laboratory supplies, materials, and other expenses		190,915,000		4,313,000
Subtotal				17,032,000
2. Research Management and Support:				
a. Within grade increase		54,468,000		997,000
b. Annualization of January 2000 pay increase		54,468,000		667,000
c. January 2001 pay increase		54,468,000		1,511,000
d. One day less pay		54,468,000		(221,000)
e. Payment for centrally furnished services		6,247,000		262,000
f. Increased cost of laboratory supplies, materials, and other expenses		43,547,000		1,036,000
Subtotal				4,252,000
3. Cancer Prevention and Control:				
a. Within grade increase		35,421,000		648,000
b. Annualization of January 2000 pay increase		35,421,000		434,000
c. January 2001 pay increase		35,421,000		983,000
d. One day less pay		35,421,000		(144,000)
e. Payment for centrally furnished services		1,821,000		76,000
f. Increased cost of laboratory supplies, materials, and other expenses		64,849,000		1,465,000
Subtotal				3,462,000
Subtotal, Built-in				24,746,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes--continued

CHANGES	2000 Current Estimate Base No.	2000 Current Estimate Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,930	973,862,000	252	119,076,000
b. Competing	1,200	360,626,000	(12)	3,607,000
c. SBIR/STTR	329	68,098,000	0	2,159,000
Total	4,459	1,402,586,000	240	124,842,000
2. Centers	84	216,566,000	0	6,498,000
3. Other research	890	268,443,000	0	5,869,000
4. Research training	1,675	59,781,000	0	714,000
5. Research and development contracts	107	203,211,000	0	12,621,000
Subtotal, extramural				150,544,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes		435,511,000		714,000
b. Special emphasis areas		8,545,000		0
Subtotal, intramural	1,847	444,056,000	51	714,000
7. Research management and support	735	104,262,000	0	(84,000)
8. Cancer prevention and control	275	364,788,000	0	7,117,000
9. Construction		3,500,000		(500,000)
Subtotal, program		3,067,193,000		157,791,000
Total changes	2,857		51	182,537,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Budget Authority by Object

	FY 2000 Estimate	FY 2001 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	2,857	2,908	51
Full-time equivalent of overtime and holiday hours	14	14	0
Average ES salary	$126,075	$130,800	$4,725
Average GM/GS grade	11.1	11.1	0
Average GM/GS salary	$59,703	$61,900	$2,197
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$60,253	$62,500	$2,247
Average salary of ungraded positions	$74,667	$77,429	$2,762

	OBJECT CLASSES	FY 2000 Estimate	FY 2001 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$134,969,000	$144,525,000	$9,556,000
11.3	Other than Full-Time Permanent	33,037,000	35,676,000	2,639,000
11.5	Other Personnel Compensation	10,271,000	11,044,000	773,000
11.8	Special Personnel Services Payments	34,197,000	36,952,000	2,755,000
11.9	**Total Personnel Compensation**	**212,474,000**	**228,197,000**	**15,723,000**
12.0	Personnel Benefits	47,846,000	51,359,000	3,513,000
13.0	Benefits for Former Personnel	13,000	14,000	1,000
	Subtotal, Pay Costs	**260,333,000**	**279,570,000**	**19,237,000**
21.0	Travel & Transportation of Persons	4,758,000	4,813,000	55,000
22.0	Transportation of Things	963,000	974,000	11,000
23.1	Rental Payments to GSA	3,000	3,000	0
23.2	Rental Payments to Others	4,798,000	4,872,000	74,000
23.3	Communications, Utilities & Miscellaneous Charges	6,287,000	6,424,000	137,000
24.0	Printing & Reproduction	5,057,000	5,167,000	110,000
25.1	Consulting Services	17,964,000	18,175,000	211,000
25.2	Other Services	107,989,000	107,044,000	(945,000)
25.3	Purchase of Goods & Services from Government Accounts	221,215,000	249,457,000	28,242,000
25.4	Operation & Maintenance of Facilities	43,207,000	42,624,000	(583,000)
25.5	Research & Development Contracts	238,592,000	242,876,000	4,284,000
25.6	Medical Care	3,110,000	3,128,000	18,000
25.7	Operation & Maintenance of Equipment	5,954,000	6,029,000	75,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**638,031,000**	**669,333,000**	**31,302,000**
26.0	Supplies & Materials	34,066,000	34,147,000	81,000
31.0	Equipment	26,917,000	27,042,000	125,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	2,085,970,000	2,217,385,000	131,415,000
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	10,000	0	(10,000)
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**2,806,860,000**	**2,970,160,000**	**163,300,000**
	Total Budget Authority by Object	**3,067,193,000**	**3,249,730,000**	**182,537,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Salaries and Expenses

OBJECT CLASSES	FY 2000 Estimate	FY 2001 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$134,969,000	$144,525,000	$9,556,000
Other Than Full-Time Permanent (11.3)	33,037,000	35,676,000	2,639,000
Other Personnel Compensation (11.5)	10,271,000	11,044,000	773,000
Special Personnel Services Payments (11.8)	34,197,000	36,952,000	2,755,000
Total Personnel Compensation (11.9)	**212,474,000**	**228,197,000**	**15,723,000**
Civilian Personnel Benefits (12.0)	47,846,000	51,359,000	3,513,000
Benefits to Former Personnel (13.0)	13,000	14,000	1,000
Subtotal, Pay Costs	**260,333,000**	**279,570,000**	**19,237,000**
Travel (21.0)	4,758,000	4,813,000	55,000
Transportation of Things (22.0)	963,000	974,000	11,000
Rental Payments to Others (23.2)	4,798,000	4,872,000	74,000
Communications, Utilities and Miscellaneous Charges (23.3)	6,287,000	6,424,000	137,000
Printing and Reproduction (24.0)	5,057,000	5,167,000	110,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	17,964,000	18,175,000	211,000
Other Services (25.2)	107,989,000	107,044,000	(945,000)
Purchases from Govt. Accounts (25.3)	79,153,000	81,290,000	2,137,000
Operation & Maintenance of Facilities (25.4)	9,564,000	9,686,000	122,000
Operation & Maintenance of Equipment (25.7)	5,954,000	6,029,000	75,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**220,624,000**	**222,224,000**	**1,600,000**
Supplies and Materials (26.0)	33,353,000	33,428,000	75,000
Subtotal, Non-Pay Costs	275,840,000	277,902,000	2,062,000
Total, Administrative Costs	**536,173,000**	**557,472,000**	**21,299,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

Fiscal Year 2000 House Appropriations Committee Report Language (H. Rpt.106-370)

Item

Cancer Coordination --The Committee encourages NCI to continue its leadership role as coordinator of the National Cancer Program. As the facilitator of the Nation's fight against cancer, the Committee encourages NCI to continue to work in collaboration with private and voluntary sector organizations, the Centers for Disease Control and Prevention, and other federal agencies to address the coordination challenges outlined in the National Cancer Advisory Board's report entitled *Cancer at a Crossroads.* (p. 67)

Action taken or to be taken

In 1999, approximately 1.2 million cases of cancer were diagnosed in the United States, and approximately 563,100 Americans died of their disease -- more than 1500 people each day. Despite the very real and tangible progress that has been made against cancer -- the rate of new cancer cases declined an average of nearly one percent per year between 1990 and 1996, while the cancer death rate fell, on average, 0.6 percent per year during the same period -- cancer remains the second leading cause of death in the Unites States, second only to heart disease. For many Americans, it remains the most feared of all diseases.

The Nation’s response to the burden of cancer is led and coordinated by the National Cancer Institute (NCI). In 1937, the National Cancer Institute was established within the Public Health Service and the Surgeon General was directed to promote coordination of research conducted by the NCI and other agencies, organizations, and individuals. In 1971, the National Cancer Act expanded and intensified “a coordinated cancer research program encompassing the programs of the NCI, related programs of other research institutes, and other federal and non-federal programs.” At that time, the NCI Director was charged with overall coordination responsibility of what would come to be called the National Cancer Program.

In 1993, the Congress requested that a “knowledgeable and independent panel” assess the achievements of the National Cancer Program and put forth a new plan to carry the Program into the next century. In response, the NCI, through a subcommittee of the National Cancer Advisory Board (the Subcommittee to Evaluate the National Cancer Program, or SENCAP), began a comprehensive evaluation of the National Cancer Program. The SENCAP completed its report, entitled *Cancer at a Crossroads: A Report to Congress for the Nation*, in 1994. In this report, the SENCAP made 37 recommendations intended to strengthen the NCP, beginning with four overarching recommendations dealing with coordination, evaluation, funding, and the Cancer

Centers program. Here, only those activities of the NCI related to coordination will be highlighted.

The National Cancer Program (NCP) is broad, encompassing the research programs of the NCI and relevant programs of other National Institutes of Health (NIH) institutes, centers, and divisions, federal agencies, and non-federal organizations. Coordination of these diverse areas calls for exchange of information, avoidance of unnecessary overlap and duplication, support of the many areas of expertise needed to overcome cancer, and recognition and stimulation of research opportunities that lead to understanding the etiology and biology of cancer and thus provide the means to control and prevent it. Although coordination of the NCP is not an outgrowth of a Presidentially-led plan *per se* as originally envisioned by the SENCAP, the Administration has made a strong commitment to such coordination and actively supports it through funding of the NCI, other agencies that conduct cancer research (e.g., the Department of Defense, the Centers for Disease Control, etc.), and such advisory bodies as the National Cancer Policy Board (see below).

NCI's coordination of the NCP has grown markedly stronger since the publication of *Cancer at a Crossroads* in 1994. Because of the breadth and diversity of the NCP, "top-down" management of resources across a broad spectrum of agencies is impossible. Instead, the NCI coordinates the NCP through active partnership and cooperation with other agencies and the national cancer community. NCI's coordination strategy emphasizes inclusion of all major stakeholders in the cancer research enterprise: for example, there are consumers/advocates as members on all standing NCI advisory bodies, on ad hoc advisory groups, and on the peer-review panels that evaluate the science contained in grant applications solicited via Requests for Applications (RFAs) from NCI that relate to patient-oriented and population-based research.

In the past five years, the NCI has undertaken a number of initiatives that enhance its coordination role. These include:

The National Cancer Policy Board

The NCP involves more than research, but the needs of the NCP have exceeded those delimited by statue and the scope and authorities of the Federal Government. For optimal dealing with the national questions related to cancer, changes in public policy, as well as societal changes and individual lifestyle changes, will be required. These clearly extend beyond the realm of federal cancer research programs. A course must be charted that identifies current limitations and builds upon a vital NCP to extend it beyond research to its application to all people and to include non-research, non-governmental, and community constituents whose actions impact the cancer problem.

For these reasons, the NCI Director requested that the National Academy of Sciences through the National Research Council's Commission on Life Sciences and the Institute of Medicine establish the National Cancer Policy Board (NCPB). The NCPB was launched using NCI funds; the Centers for Disease Control and Prevention has also participated in funding this effort through an interagency agreement between the CDC and NCI. The NCPB brings together

constituencies concerned about cancer control with those who conduct research and deliver health services. Members are individuals with diverse expertise who have distinguished themselves, earning the respect and trust of one or more cancer constituencies.
The NCPB is intended to confront obstacles and address issues that arise in the prevention, control, diagnosis, and treatment of cancer. It meets at least three times annually to examine ongoing research, new technologies, issues arising in delivery of care, and problems faced in the Nation's battle against cancer. It serves as a common meeting ground for the many federal agencies that sponsor or directly conduct relevant work as well as state and local health authorities. The Board's most distinctive contribution, however, will be to render advice to the Nation in the area of policy and make recommendations to advance the Nation's effort against cancer. To date, the NCPB has issued two major reports: *Taking Action to Reduce Tobacco Use* (1998) and *Ensuring Quality Cancer Care* (1999).

The Bypass Budget

The Institute's Bypass Budget document, *The Nation's Investment in Cancer Research*, serves as the central planning document for the NCP, uniting the cancer research community with a common vision. Through this document, the cancer community is informed of NCI's priorities and the strategies the Institute intends to follow in working toward its goals. In preparing the Bypass Budget, NCI actively seeks input from all of its constituencies, including scientific and medical organizations and consumers/advocates.

The Common Scientific Outline

The Common Scientific Outline (CSO) is as its name indicates, a simple outline that allows the Institute to organize and categorize the NCI-supported research portfolio into useful scientific topic areas. It provides the foundation for communicating the rich and complex NCI research portfolio to interested parties, including the public, the Administration, Congress, NCI staff, and the cancer research community, and it provides the potential of a shared platform among other cancer funding agencies. It is our hope that this platform will eventually be built into a national cancer research portfolio that will enhance communication and coordination across agencies and institutions nationwide; and, in fact, other cancer founders have expressed an enthusiastic interest in using the CSO to code and analyze their portfolios. The Department of Defense has committed to coding its complete portfolio to the outline, and NCI is in discussions with the American Cancer Society regarding use of the CSO for coding its portfolio. Other cancer founders will be invited to participate in using the CSO for portfolio analysis in the future.

The Quality Cancer Care Initiative

To make cancer a working model for quality of care, a DHHS trans-agency task force, the Quality of Cancer Care Committee (QCCC), is being created with two subcommittees, one to focus on the research issues and the other to concentrate on the delivery of care, with substantial coordination between them. The QCCC will build on working relationships already established in previous projects and work within the structure of the DHHS Quality Improvement Initiative. Its goals will be to ensure that the NCI's four point initiative in quality of cancer care research not only addresses the recommendations of the NCPB Report *Ensuring Quality Cancer Care*, but

that it also functions in collaboration with other federal quality of care research initiatives. In addition, its goals are to establish consistency between scientific evidence and federal resources spent in the delivery of health care (e.g., Medicare) and to ensure that the best evidence available is used in the delivery of care across the cancer continuum. Through involvement of states, professional organizations and other private sector entities, it will seek ways to apply the principles and practice of quality of care for issues important to the public, high-risk individuals, and cancer patients.

Industrial Relations

Significant discovery takes place in the private sector, and over the past four years NCI has greatly strengthened its relations with private industry. A new coordinating office within the NCI has been created, and a number of initiatives have been undertaken. For example, in September 1999 the first NCI-Industry Forum and Workshop on Biomedical Imaging in Oncology convened in response to the rapid pace of innovation, discovery, and new developments in cancer research, basic science, and imaging technology. Participants represented many facets of industry, government, research, academia, and medicine. Participants in the conference agreed that a highly interactive process is needed, one that will include the major stakeholders and allow them to interact in a way that they have never interacted before. Stakeholders need to decide what to do when a promising new technology comes along that the nation needs, and none group can develop it alone. NCI has a history of relationships with pharmaceutical and device companies that can help in any sharing necessary; the Institute can also work with industry through trade associations. In addition, NCI can play an important coordinating role in the advancement of imaging not only through research but by serving as a convener and as an organizer.

Liaison Activities

The NCI Office of Liaison Activities (OLA) was established to strengthen NCI relationships with cancer-related advocacy and voluntary organizations. The OLA coordinated the formation of a new NCI Director's Consumer Liaison Group (DCLG), consisting of 15 consumer-advocates who are involved in cancer advocacy and/or volunteer organizations that will meet several times each year with the Director of the NCI. The DCLG is helping to develop and establish mechanisms for identifying appropriate consumer-advocates to serve on key advisory bodies to the NCI. The DCLG is also participating in discussion of the broad development of NCI programmatic and research priorities, such as the development of the annual Bypass Budget. The DCLG also serve as a conduit for communication and facilitate the maintenance of a strong partnership between the NCI and the consumer-advocate community. In the recent study of priority setting at the NIH conducted by the Institute of Medicine, the NCI DCLG was sited as exemplary of how consumer input might be integrated.

To strengthen relationships with professional societies and federal agencies, OLA is organizing and hosting regular meetings between senior NCI staff and leadership of these groups. Through these meetings, the institute can exchange views, discuss programs, identify common goals, and coordinate activities to share resources and capitalize on the strengths of each organization. These meetings have been very successful in helping NCI to learn about the concerns of the

organizations, to begin an ongoing dialogue about the programs of the institute, and to assist the organizations in teaming about specific topics or activities. The OLA has also coordinated meetings with federal agencies including the CDC to 1) identify areas where NCI and CDC have ongoing collaborations; 2) determine what made those joint efforts succeed; and 3) discuss future collaborations.

Specific initiatives with other agencies

For example, NCI and the Health Care Financing Administration formed a partnership to raise awareness about regular mammography screening among women ages 65 and older, and of the expanded mammography screening benefit for Medicare beneficiaries. The partnership's efforts have been expanded to work with medical organizations to increase awareness among providers, facilitate communication between providers and patients about mammography and breast cancer, and increase the number of providers who refer female Medicare beneficiaries ages 65 and older for screening mammograms, with a concerted effort to reach those physicians who treat minority women. NCI also collaborates with the CDC on a number of initiatives, including surveillance programs and tobacco control initiatives; the Department of Defense on breast cancer research; and the Department of Energy and the Nuclear Regulatory Commission on studies related to the cancer-associated effects of the Chernobyl nuclear power plant accident and the nuclear weapons programs of the former Soviet Union.

Advisory Boards and Groups

To ensure the wise use of resources to meet the goals of the National Cancer Program, NCI actively seeks out expert advice from a variety of advisory bodies both within and outside the Institute. These include the National Cancer Advisory Board, which advises NCI's Director on issues related to the entire National Cancer Program; the Board of Scientific Counselors (BSC), which advises the NCI on the progress and future direction of NCI's Intramural Program; and the Board of Scientific Advisors (BSA), which represents the cancer research community's voice. Both the BSA and the BSC are composed of distinguished representatives from outside the NCI, and both include members of the consumer advocacy community.

Requests for Applications (RFAs)

Once most commonly issued to solicit projects from individual investigators, RFAs are increasingly being used to develop consortiums and partnerships rather than more traditional individual research project grants. For example, the Cancer Genetics Network, the Early Detection Research Network, the Cooperative Prostate Cancer Tissue Resource, and the *In Vivo* Cellular and Molecular Imaging Centers are all RFA-driven. Using this mechanism, NCI is achieving coordination in a variety of scientific areas.

Progress Review Groups (PRGs)

PRGs are composed of prominent members of the scientific, medical, and advocacy communities who know the state of the science intimately and can provide a thoughtful, considered assessment of the NCI portfolio and recommend activities that will speed our progress. The

overall goal of the PRGs is to provide recommendations for a national cancer research agenda. PRGs meet regularly over a period of months to review an NCI-prepared analysis of the Institute's current research program, review recommendations from the research and advocacy communities, define and prioritize unaddressed scientific opportunities that should be pursued, and to develop a plan of action for the research area. In the past year, PRGs in Breast and Prostate Cancer completed their assessments of NCI research programs and we have begun considering and implementing their recommendations. A Colorectal Cancer PRG has been initiated, with a large-scale Roundtable meeting scheduled for January 2000. PRGs covering brain tumors, pancreatic cancer, and lymphoma are planned for the coming year.

Program Reviews

NCI supports research through a variety of mechanisms, many of which provide funds tailored to specific research processes. As part of an ongoing process of review and revitalization, NCI has instituted a series of external reviews to guide us in strengthening our major research support programs. In the past few years, we have completed in-depth reviews of several programs: Cancer Centers, Cancer Control, Clinical Trials, Cancer Prevention, and the Developmental Therapeutics Program.

Implementation Groups

Program reviews, progress reviews, and other assessment and advisory activities conducted at NCI generate not only insights, but also recommendations concerning how best to organize a program or pursue a field of research. Implementing these recommendations is key to successful planning, as planning alone does not bring about change. To implement changes, we have formed groups of outside scientists and NCI staff that grapple with the redesign of programs and development of new initiatives that are recommended by the Program Review Groups, Progress Review Groups, and extraordinary opportunity Working Groups. Ongoing Implementation Groups include those focused on Clinical Trials, Prevention, Surveillance, Diagnostics, Tobacco Research, and Early Detection.

Outside agencies and advisory/oversight bodies frequently produce reviews of some part of the NCI or the NCP. Recent examples of these include the two reports from the National Cancer Policy Board and the Institute of Medicine's report on the unequal burden of cancer. Governmental bodies such as the General Accounting Office may also evaluate components of the NCI/NCP. NCI welcomes the insight of these groups and strives to respond to their recommendations through programmatic and operational changes, where appropriate.

Other Collaborations with CDC

In 1997, NCI and CDC staff met to discuss current collaborations between the two federal agencies and the establishment of working groups related to a variety of issues and activities. After much discussion, representatives from both CDC and NCI agreed that establishing formal working groups might not be needed at this time. Instead, an umbrella working group has been holding annual meetings to brief appropriate CDC and NCI staff about progress made in current activities, as well as to discuss future collaborations. Joint projects will continue on a more

informal basis. CDC and NCI agreed to identify points of contact for specific areas of collaboration to ensure follow up.

The goals of expanded collaborations include increased:

- Communication
- Opportunities for joint efforts
- Coordination of efforts -- using resources for complementary efforts
- Partnerships -- each agency has contacts with groups that may be unique; these can be brought together so that more diverse federal and private sector
- Groups are included in discussions and projects

The two agencies agreed to collaborate on reports such as a summary of federal legislative activities that affect state health departments, and other issues related to cancer detection, diagnosis, treatment, control, and prevention including the impact of genetic testing on the health insurance industry.

Current and Ongoing NCI/CDC Collaborations and Plans for the Future

Prostate, Lung, Cervical, and Ovarian Cancer Screening Trial (PLCO)

Collaborations to increase participation in this screening trial have been under way for some time. CDC and NCI have awarded a contract modification to identify strategies that will enhance accrual of minorities to the trial. NCI and CDC are supporting 3 PLCO projects through a memorandum of understanding:

- Henry Ford Health System PLCO Screening Center in Detroit--a small study to identify effective ways of reaching African-American men;
- Pittsburgh PLCO Screening Center--a study on the factors affecting older African Americans and cancer screening, and;
- The University of Alabama-Birmingham to operate a minority-focused screening center for the PLCO Trial. CDC is interested in looking at the value and effectiveness of various recruitment strategies, while NCI will be assessing the effectiveness of screening in reducing mortality from these cancers. Evaluation projects are included in these joint efforts.

Cancer Information Service (CIS) Outreach Project, 5-A-Day

Between 1995 and now, NCI and CDC have collaborated on efforts to improve access of underserved populations to the CIS through work with state health departments. NCI is interested in the ability of the CIS to reach these populations with these messages and how to better use CIS as a resource. NCI and CDC collaborated on an ad in that ran in Family Circle to encourage consumption of 5 fruits and vegetables a day.

Cancer Information Service and Breast Cancer Screening

The NCI is partnering with the CDC to insure the best utilization of federal resources for breast and cervical cancer screening services provided by CDC through its state health department grantees. The CIS provides educational materials and assistance in promoting the screening program to the public. CDC gave NCI funds to hire four new Outreach Coordinators to support the CDC programs in Massachusetts, Arkansas, Washington, and Illinois.

Genetics

Genetics is a relatively new area of collaboration. NCI is providing support for a DNA repository that is being established as part of the CDC supported National Health and Nutrition Examination Survey (NHANES) III. This repository will be available for studying genetic polymorphisms in about 1,000 people. In addition, feedback from consumer-advocates is needed to learn about the appropriateness of genetic testing through this mechanism. CDC is also working with the NCI to write a genetics primer that will describe and explain genetic epidemiology for advocates. NCI staff are developing genetic education materials in collaboration with CDC.

Radiation

An NCI collaboration with the CDC and the Veterans Administration (VA) focuses on the updating of radioepidemiologic tables. These tables, originally prepared by NCI, present data linking risk for cancer to exposure to radioactive materials and are based on complicated calculations and risk assumptions. The VA is requesting the updating of information because the original tables date back to the mid 80's. The joint venture between NCI and CDC will be ultimately implemented by CDC to include risk from all diseases or conditions that may result of radiation exposure.

Cancer Surveillance, Year 2000 National Health Interview Survey Supplement (NHIS)

Collaborations have been under way for several years and have included the American Cancer Society, the American College of Surgeons, and the North American Association of Central Cancer Registries (NAACCR). One project involves an attempt to answer several key questions: 1) what is cancer surveillance?; 2) what information is missing?; and 3) how is the data used? Other projects include developing standard protocols for data collection that includes non-hospital (out-patient) sources, and both CDC and NCI funded sites.

Cancer Surveillance

For over 25 years, the National Cancer Institute has supported the Surveillance, Epidemiology, and End Results (SEER) Program. The SEER Program is the acknowledged standard for excellence in providing high quality data on cancer statistics and has been the source for estimates of national data on cancer incidence, survival, and mortality and trends in these statistics for many years. SEER currently includes five states and six regions within other states that together cover about 14% of the United States population. The National Program for Cancer

Registries (NPCR) at the CDC was mandated by Congress in 1992 to expand the capability for cancer surveillance through state registration for the entire United States. This program currently serves 45 states, three territories, and the District of Columbia in attempts to build or enhance state needs for cancer surveillance. The DCCPS Surveillance Research Program has been working with the CDC directly and through the North American Association of Central Cancer Registries (NAACCR) to advance the need for a coordinated national cancer surveillance system that builds on the strengths of both federal activities. Including SEER, approximately 30% of the country now reaches a NAACCR "gold-silver" quality standard.

The NCI is implementing recommendations from the Institute of Medicine and it's own Surveillance Research Implementation Group to expand the coverage of SEER to include populations currently under-represented by the SEER Program (e.g., American Indians, Hispanics, and rural African-American and white populations). The NCI and the CDC are currently developing a Memorandum of Understanding that defines the separate and joint roles of these agencies in national cancer surveillance, including how they will work together to support the expansion of SEER, the enhancement of the NPCR, technical support to upgrade state registries, and joint dissemination of cancer surveillance information.

Surveillance Activities in Applied Research

In addition to cancer registration in SEER and NPCR, the NCI and CDC are involved in numerous activities that require linkages with or the use of databases maintained by each agency.

Risk Factor and Screening Surveillance

Both the NCI and the CDC provide funds for the development and implementation of the CDC's National Center for Health Statistics (NCHS) National Health Interview Survey (NHIS) Cancer Control Topical Module. The next survey is for the year 2000. This has been a very collaborative and constructive relationship. The California Health Information Survey (CHIS) is a special survey initiated by the California Department of Health Services, UCLA and others that will provide additional data including a larger sample of minority respondents. NCI is providing about $2 million for this effort with CDC adding a little less than a quarter of that.

Dietary Surveillance

The National Health and Nutrition Examination Survey (NHANES) is a rich source of data on dietary practices that includes the collection of biospecimens. NHANES is supported by CDC's NCHS. NCI staff have been asked frequently to contribute to proposals to improve and expand the scope of the dietary data collected within NHANES.

Colorectal Cancer Screening Surveillance

Interest in expanding what is known about colorectal cancer screening has led to the generation of three national surveys of primary care physicians, gastroenterologists, and health plans in the DCCPS Applied Research Program. While the NCI has taken the lead in conducting these surveys, the CDC and Health Care Financing Administration are co-sponsors and will share in

the analysis and dissemination of results when the surveys are completed next year. DCCPS is working closely with CDC staff to implement this survey. The study will obtain current, nationally representative data on the physician and health system factors that may influence the use of screening and diagnostic follow-up for the early detection of colorectal cancer in community practice. Study participants are primary care physicians who are likely to administer colorectal cancer screening tests to adult patients or to refer patients to specialty physicians for such tests; specialty physicians who are likely to conduct colorectal cancer screening as well as diagnostic follow-up and surveillance procedures for suspected colorectal cancer; and health plan medical directors.

Quality of Cancer Care

Based on over ten years of experience in patterns of care and other quality oriented studies, the NCI is taking a lead on making cancer a model for the translation of research into application in health care delivery as part of Secretary Shalala's Quality Improvement Initiative (QII). Under the overall leadership of the Agency for Healthcare Research and Quality (AHRQ), the NCI is forming a Quality of Cancer Care Committee (QCCC) that will include participation from the CDC and AHRQ as well as other federal agencies such as HCFA, HRSA, IHS, VA, Department of Defense, and the FDA. The goals of this committee will be to coordinate federal cancer research activities with federal health care delivery activities to ensure that decisions on cancer services covered by the Federal Government will be consistent with the best scientific evidence available on quality outcomes.

Tobacco Control Research

Tobacco Control

Joint efforts have been under way for many years. Currently programs, including ASSIST and IMPACT, are under way. Of primary importance are efforts to prevent young people from beginning to use tobacco products.

Transfer of ASSIST

NCI staff worked with the CDC to develop the RFP to states that will support the transfer of effective state and community-level interventions as developed under the ASSIST program to CDC control.

Tobacco Control Surveillance

The NCI has pioneered many of the methods in this area for tobacco prevalence and consumption as well as more recent approaches to tracking the societal influence of policy, legislation, and local ordinances on smoking behavior. As part of the ASSIST evaluation newer methods for surveillance are being developed and evaluated. Many of these measures have been recognized as valuable and recommended for further research and monitoring by the NCI's Surveillance Research and Applied Research Programs. Continuing research on the best methods for tobacco control interventions, especially at the state and community level will

require continuing surveillance activities such as have been supported during the ASSIST program. One of these tools is the NCI-supported tobacco supplement to the Current Population Survey (CPS) at the Census. CDC would also like to be able to use these data on an ongoing basis, and the two agencies are currently working out how and under what circumstances this can be done. There are other sources of tobacco control information that are managed by the CDC (Youth Tobacco Survey and Youth Behavioral Risk Factor Survey) and the NCI (e.g., State Legislative Database and a media database), results of which can be shared.

Nutrition Research and 5-A-Day

A successful and rather close collaboration exists between the NCI's 5-A-Day program and the CDC. The results of intervention research supported by the 5-A-Day program have been picked up by CDC programs for application at the state and local level. This has been primarily accomplished through InterAgency Agreements with NCI funding. NCI staff have provided substantial input toward the development of RFAs for the CDC and in the on-going monitoring and evaluation of the state-generated interventions funded in this manner.

Guide to Community Prevention Services

Based on the Guide to Clinical Prevention Services the development of a guide for community prevention services has been proceeded under CDC leadership for the last year or so. DCCPS leadership has contributed in weekly meetings and the Division has provided modest funding to assist in the process of synthesizing research results to be summarized in the guide.

RFA/PA Collaborations

The Epidemiology and Genetics Research Program collaborated as a co-sponsor on four CDC initiatives (listed below) led by the National Institute of Occupational Safety and Health (NIOSH) within CDC. The NCI component supported advancement in environmental and/or occupational exposure assessments for epidemiologic studies of cancer.

- RFA OH-99-002, "Implementation of the National Occupational Research Agenda" EGRP/NCI funded three applications in September 1999.
- RFA OH-99-003, "Mechanistic-Based Cancer Risk Assessment Methods" EGRP/NCI funded one application in September 1999.
- PA 99-143, "Occupational Safety and Health Research," Issued August 18, 1999; first applications will be received in fiscal year 2000.
- PA 99-148, "Research Methods for Occupational Cancer," Issued August 19, 1999; first applications will be received in fiscal year 2000

DES

NCI/DCCPS is collaborating with CDC on the initiation of the National DES Education Campaign. NCI funded five cooperative grants to develop models and materials that are now being used in the development of the CDC campaign. NCI is publishing a provider handbook which describes the approved algorithm for care of women who were DES exposed. The

Institute also has supported the development of patient information booklets which the CDC plans to modify and include in their campaign. NCI continues to participate fully in the planning of the development of the campaign.

Cancer Screening

On December 9 and 10, 1999, the Behavioral Research Program/DCCPS sponsored a meeting for grantees on colorectal cancer screening behavioral research. Attendees were grantees from DCCPS, the Division of Cancer Prevention, CDC, and the American Cancer Society. There were several outcomes from the meeting including the formation of two subcommittees, one to look at the development of common measures on screening behavior across studies. A second subcommittee will be looking at the development of an algorithm to disseminate risk and guidelines to patients and providers. A listserv was established to facilitate communication among the group. Six members of the grantee meeting will be at the NCI Colorectal Cancer Progress Review Group meeting in San Francisco January 5-7, 2000. This is the first meeting for all behavioral researchers on the topic of behavioral research in colorectal cancer screening.

Breast Cancer Screening

A third area of information exchange has been in the area of breast cancer screening where CDC staff involved in evaluation of data from the CDC Breast and Cervical Cancer Detection Program, have participated periodically in meetings of the NCI Breast Cancer Surveillance Consortium to be informed about these efforts to evaluate the performance of screening mammography in community practice.

Cancer Communications

The NCI and the CDC are collaborating on a campaign to alert Americans alive in the 1950s and 1960s that they were exposed to radiation fallout (I-131) as the result of government sponsored tests of atom bombs at the Nevada Test Site. The campaign will inform people of their exposure, describe the possible health consequences of such exposure, and provide information that will help exposed individuals decide whether or not to undergo health screening. The NCI is leading the first part of this effort. It is working intensively with representatives of exposed communities to conduct consumer research and then develop a strategic communications plan. CDC is involved in this early effort, but will take the lead in implementing the campaign. NCI will assist in the implementation.

The NCI is financing a CDC campaign to educate health professionals and the public about possible exposure to diethylstilbestrol, used between 1940 and 1971 in a vain attempt to prevent miscarriages. Some daughters and sons born to mothers who took DES are at higher risk for some cancers and other diseases, and the mothers are thought to be at increased risk of breast cancer. There is also concern that grandchildren of mothers who took DES may have elevated risk for certain health problems. CDC is now planning the campaign and will launch it during 2000. NCI staff are part of the planning group, which includes members of the advocacy community.

The CDC is conducting national education programs for the public and health professionals about colorectal cancer, melanoma, and prostate cancer. The NCI is supporting these programs by reviewing messages for accuracy and appropriateness, by allowing CDC to promote use the Cancer Information Service for individuals who want more information, and by distributing CDC-developed materials through NCI networks.

NCI and CDC are in the process of evaluating a three-year demonstration project between NCI's Cancer Information Service and CDC's National Breast and Cervical Cancer Early Detection Program. The purpose of the project was to increase mammography screening rates among medically underserved, rural, African-American, Hispanic, and American Indian women in Washington State, Massachusetts, Arkansas, and Illinois. If the evaluation shows that the project has been successful, the two agencies will explore future opportunities to collaborate on the local and state levels.

Item

Cancer Demographics --The Committee is concerned by cancer incidence projections relative to the aging of the population. Based on current incidence rates, new cases of cancer and cancer deaths are estimated to increase by 29 percent and 25 percent, respectively, by 2010. The Committee looks forward to hearing from the Director of the Institute at the fiscal year 2001 appropriations hearing on what steps should be considered in order to address the changing demographics of cancer in this country. (p.67)

Action taken or to be taken

Aging of the U.S. population and of other major industrial nations is a trend that continues to reshape our global demographic, social, economic, political, and cultural structures. Longer life spans, dramatic changes in disease patterns, and the ongoing revolution in biotechnology are reshaping health-related perspectives. Within this broader context and coupled with simultaneous changes in the racial and ethnic composition of our populations, national trends in the U.S. cancer burden are in flux.

Many times it is difficult to understand the inter-relationships of the burden of the disease on a population and the risk of having/dying of a disease. Cancer is predominantly a disease of older Americans with 60 percent of all diagnosed cases and 70 percent of all cancer deaths occurring among persons 65 years and older. The median age at cancer diagnosis is 68 years of age and at 71 years of age for cancer death. A recent article showed that between 1990 and 1996, cancer incidence rates decreased an average of about 1 percent per year and mortality decreased an average of 0.6 percent per year. While the rates have decreased, the trends in number of cancer cases is more unpredictable, and the number of cancer deaths has increased because there are more people in the United States and the population is aging.

Within the National Cancer Institute (NCI), the cancer surveillance research program collects and disseminates information on the changing U.S. cancer trends. The NCI SEER (Surveillance, Epidemiology, and End Results) Program is the most authoritative source of information on cancer incidence and survival. The SEER database has more than 2.5 million cases diagnosed

between 1973 and 1997 from residents of selected regions that represent approximately 14 percent of the U.S. population. Geographic areas were selected for inclusion in SEER based on their ability to operate and maintain a high quality population-based reporting system and for their diverse population subgroups. The SEER areas are comparable to the general U.S. population with regard to measures of poverty and education, but tend to be more urban and have a higher proportion of foreign-born persons.

In 2000, the NCI surveillance efforts are being expanded to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. SEER will add up to 4 new population-based registries in geographic areas where minorities and medically underserved populations live. Of particular interest are groups such as rural African Americans, Hispanics from Caribbean countries, American Indians, and residents of Appalachia and other rural areas, especially those of lower socioeconomic status. Expansion will also include coverage of states that have high cancer mortality rates. To complement this geographic expansion, the NCI will fund technical assistance to 7-21 other population-based registries to upgrade data collection, management, quality control procedures, and information technology tools. These initiatives are designed to improve our national cancer surveillance infrastructure and provide high-quality cancer incidence data used in analysis and reporting based on SEER and non-SEER registry systems. Current collaborations among the NCI, Centers for Disease Control and Prevention, American Cancer Society, North American Association of Central Cancer Registries, and National Center for Health Statistics will be enhanced to produce national, state, and regional specific data.

The mortality data reported by the NCI surveillance program are provided by the National Center for Health Statistics for the entire U.S. population.

When the U.S. cancer mortality rate for 1997 is compared to 1990, there was a decline of 5.6 percent while the numbers of deaths increased 6.8 percent due to the population increasing 7.3 percent and the aging of the population. The under 65 age group increased 7.0 percent while the 65+ age group increased 9.5 percent. The declines in cancer mortality were larger in the younger age groups. Overall, the cancer mortality rate declined 11.5 percent for those under 65 in contrast to declining 1.8 percent for those 65 years of age and older. The SEER cancer incidence patterns for the period 1990-1996 varied by sex and age at diagnosis. The largest annual decreases in incidence rates for all sites combined occurred in males who were 25-44 years old and males who were 75 years old and older at diagnosis. Age-specific trends in females were less remarkable, with the only significant decline among those 35-44 years old.

Demographers have projected that the population will continue to increase and to age. Between 1997 and 2010, the population will increase 11.2 percent; the <65 age group will increase 10.6 percent and the 65+ age group will increase 15.2 percent. Unless there are really steep declines in the cancer incidence and mortality rates, this means that we will continue to see increases in the overall numbers of cases and deaths. This also means that cancer will continue to be an increasing burden on our health care systems for the foreseeable future.

Current Activities

- A study at Harvard focuses on the age-related impact of breast cancer on physical and psychosocial function, comparing older and younger women.
- A cohort study in Iowa study addresses potentially modifiable risk factors for breast cancer in older women, and another project is assessing the effect of exercise breast cancer risk in older women. Multiple studies assess endogenous hormone levels in older women and breast cancer risk.
- A series of projects is addressing the adverse effects, protective effects, and risk modification by therapeutic drugs, both by prescription and nonprescription, taken by older men and women, since medication use increases with age. One study assesses commonly used medications and breast cancer risk in a biracial population. Another project focuses on calcium channel blockers, increasingly used for hypertension and coronary disease in older women, as well as other medications, and the risk of breast cancer. Other projects are looking at postmenopausal hormone therapy in older women and the risk of endometrial cancer, large bowel cancer, mammographic density changes, and breast cancer in multiple ethnic groups.
- Prostatic intraepithelial neoplasia (a potential precursor of prostate cancer) is being studied in older men in several different ethnic groups.
- Total hip or knee replacement becomes more common with aging. One project is studying hip or knee replacement with devices containing chromium, to assess the degree to which DNA-protein crosslinks are generated, a sign (biomarker) of biologic damage from chromium exposure.
- A large follow-up study is looking for predictors of general cancer mortality in an aging cohort first studied over thirty years ago.
- Several cancer-screening studies are developing behavioral interventions to overcome older women's barriers to getting screened for breast and cervical cancer.
- The NCI has joined with the National Institute on Aging (NIA) to conduct two studies on aging and cancer. The first study was a retrospective review of medical records to assess other conditions that lead to morbidity in three age strata (55-64, 65-74 and 75+ years of age) of cancer patients. The second study is an illness behavior study, which includes patient interviews to assess comorbidity and functional status. Several analyses have been published on the first study and other analyses are in progress. The second study has completed data collection. The major objectives of these studies are to develop descriptive information in response to two basic questions: 1) What are the predominant comorbid conditions and functional limitations for older persons with cancer? And 2) What do older persons do when they become aware of having suspicious signs and symptoms?
- The SEER-Medicare database, a collaborative effort of the NCI, the SEER registries, and the Health Care Financing Administration, is a large population-based source of information for cancer-related epidemiologic and health services research. This database, which contains information on cancer cases from 1986 through 1996, allows researchers to address topics such as the economics of cancer care, patterns of care from diagnosis through end of life, variation in care across diverse health care systems, and changes in cancer care over time. In 1999, 14 articles using SEER-Medicare data have been published. The focus of these papers has included comparisons of cancer care between persons with fee-for-service (FFS) coverage versus HMO care, factors that influence the reported changes in cancer incidence,

patterns of cancer care, and methodological evaluations of the utility of Medicare claims for cancer surveillance. The findings from the HMO and fee-for-service comparisons are varied. In the case of prostate cancer, men with FFS coverage have better cancer-specific survival than men in HMOs, while for colon cancer, cancer-specific mortality was comparable between persons with FFS and HMO coverage Perhaps the most noteworthy conclusion from two of these studies is that there is considerable variation in treatment patterns between individual HMOs. As a result, findings from studies comparing care from an aggregation of HMOs with an aggregation of cases provided to person with FFS coverage may have limitations in the ability to extrapolate findings to all HMOs.

Future Activities (some already underway)

- The NCI and the NIA are jointly supporting a series of collaborative and interdisciplinary genetic epidemiology investigations. These studies are designed to identify and evaluate the interactions of genetic and epidemiologic risk factors leading to cancer susceptibility in individuals, families and populations, as well as factors influencing the rate of increase with age in cancer susceptibility. The special feature of this Request for Applications (RFA) is the support of multi-site, cooperative research applications by multi-disciplinary teams of investigators. Particular attention is to be paid to aging populations and to the genetic factors leading to older age at onset of cancer.
- A population-based cohort study has just been launched to examine the broad impact of variation in candidate genes and their interaction with environmental exposures on cancer incidence and survival specifically, and health and aging more generally. Participants, numbering 8395 people, from two blood and data specimen banks CLUE I (1974) and CLUE II (1989) comprise the study cohort. The cohort has been followed prospectively for 24 years and information on environmental factors such as smoking, education, and housing are available as far back as 1963.
- Breast cancer with an onset at older ages is probably caused by the interaction of multiple genes, endogenous environments, and exogenous exposures. One consequence of this complex, multifactorial etiology of breast cancer is that etiologic heterogeneity may exist. A recently launched project is addressing this question. Etiologic heterogeneity implies that two or more types of breast cancer in the general population may be caused by different sets of etiologic events. The ability to define etiologically-distinct (i.e., homogeneous) subgroups in the population may facilitate: 1) epidemiological studies to identify causative agents in breast cancer etiology; 2) identification of optimal breast cancer diagnosis or treatment regimens; and 3) the targeted application of cancer detection and prevention strategies. Cancer susceptibility genotypes at the cytochromes p450 and glutathione-S-transferase loci, as well as somatic genetic mutations, will be evaluated for their capacity to define etiologically heterogeneous case groups with respect to age at breast cancer diagnosis.
- Research priorities that have been identified with regard to the development of cancer in an aging population include improving the accuracy of our measurement and estimation of exposure. Particularly, historical exposures years ago in childhood, and exposures that occur long term and over the entire lifespan, to environmental agents, need to be accurately assessed. Our approaches to study design and analysis for conducting environmental research that focuses on lifespan gene-environment interactions need to be improved. This

priority area will be encouraged and supported through a Request for Applications to be issued in collaboration with NIEHS in 2000.

- A new program, the Cancer Intervention and Surveillance Modeling Network (CISNET) was initiated in 1999 with cooperative grant awards to be made early in 2000. This program supports the use of mathematical and statistical techniques to integrate and synthesize known demographic, biological epidemiological, clinical, behavioral, genetic, and economic information. Through the use of modeling techniques, researchers will investigate the impact of cancer interventions (i.e., screening and treatment) on hypothetical populations, or in trial and other clinical settings. Managed through a cooperative mechanism, CISNET will promote the application and extension of these models to population-based settings to help understand and explain observed (and future trends), particularly relevant in an aging and socio-demographically changing society. Initial research will focus on breast, prostate and colorectal cancer with the second round of applications directed toward other key types of cancer.
- Several new initiatives are being developed in 2000 to enhance the NCI surveillance systems used to identify and study cancer trends, track the impact of cancer on the general population and provide information that researchers need to ask critical questions about why certain populations are affected by cancer more severely than others. Other initiatives are under development that support new investments in surveillance research targeting specific population groups, such as the elderly, and that will make it possible to connect information on socio-demographic characteristics, prevention and other health behaviors, risk factors and exposures, screening, treatment, and patterns of care with outcomes such as incidence, quality of life, and survival.
- A Program Announcement will be released in 2000 in to stimulate exploratory research on the feasibility and utility of employing Geographic Information Systems (GIS) for geocoding surveillance data and reporting geographic relationships among screening measures, risk factors (including environmental exposures), and improved cancer outcomes. A GIS can be used to monitor cancer patterns and their changes over time and space, thus serving as a tool for surveillance, planning and evaluation of cancer control strategies, and implementing culturally relevant cancer prevention and intervention efforts in economically disadvantaged and underserved communities, including the elderly. This initiative extends the methodological and applications research illustrated by the specific initiative entitled GIS for the Long Island Breast Cancer Study Project.

Item

Cervical Cancer and Human Papillomavirus --The Committee is encouraged by the research progress that has been achieved in the development of a vaccine for the human papillomavirus (HPV) and in treatment for advanced stage cervical cancer. The need to coordinate this research both nationally and internationally should be recognized. The Committee urges NCI to initiate a strategic planning process to review, coordinate, and expand all aspects of cervical cancer research and enhance efforts to expand access to the Pap test for all women. The Committee also encourages NCI to continue its collaboration with the NIAID in sponsoring basic and clinical research on HPV diagnosis and prevention as a risk for cervical cancer. (p. 67)

Action taken or to be taken

An estimated 13,700 cases of invasive cervical cancer were diagnosed in America in 1998 and nearly 5,000 American women died of the disease. Although incidence and death rates have been declining, cervical cancer remains in the 10th most frequently diagnosed cancer in U.S. women, and over 200,000 American women are living having had a diagnosis of cervical cancer. When detected at an early stage, invasive cervical cancer is one of the most treatable cancers with a five year survival rate of 91% with localized disease. Unfortunately, only 54% of cervical cancers among white women and only 40% among African American women are diagnosed at a localized stage.

In FY 1999, NCI spent over $62 M on cervical cancer which represents nearly a 3-fold increase in spending since 1991, an increase that is significantly larger than the increase in the total NCI budget. NCI currently is funding 149 research projects related to prevention, detection, and treatment of cervical cancer. Early diagnosis and more effective prevention of cervical cancer remain a very high priority for the NCI.

Human papillomavirus (HPV) infections is one of the most common sexually transmitted diseases. Over half the adults in the United States have been exposed to the HPV virus at some point in their lives. In the vast majority of men and women, infection with this virus is transient and causes no adverse sequellae. In some individuals, however, the DNA of the virus becomes integrated into cellular DNA, and these individuals are at increased risk of developing cancer. HPV has been linked with cancers of the cervix, vagina, vulva, anus and oropharynx in women, as well as cancers of the penis, anus, and oropharynx in men. In the developed world, screening for precancerous changes with Pap smears has been associated with a dramatic reduction in the risk of cervical cancer. In the developing world, however, cervical cancer remains the first or second leading cause of cancer deaths among women in many countries.

The NCI has developed a comprehensive research program in HPV-associated disease. This program includes extensive study of the biology of HPV infection, focusing on how HPV infects normal epithelial cells, as well as the role of the HPV E6 and E7 proteins in blocking normal cellular control mechanisms. In addition, epidemiologic studies are seeking to identify nutritional, environmental, and reproductive factors which may increase the risk that HPV infection will lead to cancer. Epidemiologic and biologic studies are examing why women in some racial/ ethnic groups have particularly high rates of cervical cancer. Cervical cancer, for example, is more common among Vietnamese-American women, Native Hawaiian women, and Native American women than other populations. We are also studying the role of the immune system in fighting off HPV infection. Women with Human Immunodeficiency Virus (HIV) infection, for example, are at increased risk for developing cancer when infected with HPV.

As mentioned above, screening for precancerous changes with the Pap smear has become an accepted part of cancer prevention in the developed world. The NCI currently funds research to improve the accuracy of Pap smears, to develop new screening tests for precancerous and cancer cells in the cervix, and to improve imaging of precancerous changes in the cervix as well as invasive cancers. The NCI also is funding research to improve Pap smear screening among poor women, elderly women, rural women, and women among racial/ ethnic minorities.

The NCI currently has a partnership with Health Care Financing Administration (HCFA) to develop, implement and promote a short term joint promotion campaign to increase physician awareness of the risk of cervical cancer among Medicare aged women and to reverse the perception in the medical community that cervical cancer is not a serious health concern for women in this age group. The campaign is meant to serve as an impetus for physicians to promote regular pap/pelvic examinations among women 65 and older and will work in conjunction with other ongoing information campaigns about cervical cancer. These campaigns are targeted to women ages 18 and older with a special emphasis on minority and medically underserved women. Information was distributed through minority media outlets to African American, American Indian, Asian, and Hispanic communities. Specific publications have been translated into Spanish and are currently being adapted for the Vietnamese community through a collaboration with a group in California.

The NCI ASCUS/LSIL Triage Study (ALTS) is a large clinical trial involving more than 7000 women in 4 centers accross the US. This trial is designed to determine the optimal management plan for low-grade cervical cytologic abnormalities. One purpose of the ALTS trial is to determine whether HPV testing can effectively triage women with ASCUS/LSIL (atypical squamous cells of undetermined significance/low grade squamous lesions). The results of looking at HPV testing will inform clinicians about the risk of ASCUS/LSIL in the context of HPV infection and progression to higher-grade lesions. The results of the ALTS trial also have the potential to decrease the morbidity and costs associated with screening for precancerous changes of the cervix.

The NCI is working to evaluate new vaccines for the human papillomavirus, both as prevention and treatment for cervical cancer. These efforts include clinical HPV vaccine trials representing a trans-NIH effort that also involves the NIH Office of Women's Health, the NIH Office of Minority Health, and the National Institute of Allergy and Infectious Diseases. These trials include vaccines developed in the intramural research program of the NCI, as well as vaccines developed by industry and university laboratories. The first phase I and II trials are currently underway at NCI-designated Cancer Centers and Clinical Trials Cooperative Groups. The NCI sponsored a meeting in fall, 1998, to bring together researchers developing vaccines from academia and industry in the US and Europe, as well as representatives from the CDC and FDA. The long-term goal is to develop an effective vaccine against cervical cancer by preventing genital HPV infection and its associated disease.

One candidate immunoprophylactic vaccine being tested is a viruslike particle vaccine developed in the intramural research program of the NCI. In animal models, which involve animal papillomaviruses, such a vaccine has shown excellent type-specific protection against experimental challenge with a high dose of the homologous virus. We have recently completed an early phase safety and immunogenicity trial of normal American volunteers who were vaccinated with VLPs from HPV16, which is the HPV type found most frequently in cervical cancer. The vaccine induced an immune response in all 60 vaccinees and was well tolerated, with mild side effects consisting mainly of headache and mild temporary local pain at the injection site, as is commonly seen with other vaccines. If the vaccine continues to perform well in additional early phase testing in the United States, we plan to undertake a large scale

prospective efficacy trial of the vaccine continues to determine if the vaccine will confer protection against genital HPV infection and the cervical abnormalities it produces. A site in Costa Rica is being considered for this trial, since cervical cancer is a significant public health problem in that country and the National Cancer Institute already has an ongoing long-term natural history study of genital HPV infection and disease there. The subjects in this trial would need to be followed for several years before the efficacy of the vaccine could be determined.

The NCI's PDQ database provides information on 166 open clinical trials for cervical cancer. Of these, some 111 are NCI-sponsored trials that include 85 Phase I trials in which novel treatment approaches for cervical cancer are being tested for safety. At the other end of the development pipeline for cervical cancer treatments are 6 NCI-sponsored Phase III trials representing new treatment approaches that are closest to entering general medical practice.

The NCI currently sponsors clinical trials for women with all stages of cervical cancer. Early in 1999, five large clinical trials (all of which were sponsored by the NCI) demonstrated that show women with invasive cervical cancer benefit from a combination of radiation therapy and chemotherapy with cisplatin. These findings were the subject of a Clinical Announcement sent by the NCI to oncologists who treat women with cervical cancer in the US and the world.

The NCI is also working with the Clinical Trials Cooperative Groups and the NCI-designated Cancer Centers to evaluate and improve quality of life among cervical cancer patients and survivors. The Office of Cancer Survivorship (OCS), within the Division of Cancer Control and Population Science, has a particular focus on these issues.

The OCS is currently funding 10 different studies that will provide information about the physical, psychological, social and economic outcomes of diverse samples of adult cancer survivors. Many of these studies will include survivors of gynecologic cancer and/or provide information that will be important in identifying areas in which interventions may be needed to improve cancer survivors' health or well-being. In addition, the OCS became responsible in October 1999 for a new Mind-Body Center grant at the University of Miami that will promote psycho-oncology research across the illness and recovery continuum. This application was the result of a trans-NIH collaboration, in response to a congressional mandate that included a finding set aside, to establish centers for the Study of Mind Body Interactions and Health. One of the four projects proposed under the new center will evaluate the impact of a cognitive behavioral stress management intervention on quality of life, immune function and health outcomes for women infected with HIV and human papillomavirus at high risk for cervical cancer. Findings from this research may be helpful in elucidating not only mechanisms related to disease progression, but also potential strategies to reduce cancer risk in this population of women.

The NCI will establish a Progress Review Group (PRG) early in FY 2001 to assist in setting priorities for HPV and cervical cancer research. Like other PRGs, the cervical cancer PRG will be composed of between 21 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research. The final product of the PRG will be a report listing

research priorities and discussing the extent to which these priorities are being met. NCI will issue this report in mid FY 2002.

Item

Complementary and Alternative Medicine -- Estimates are that more than 50 percent of cancer patients include some form of complementary and alternative medicine in their treatment regime over the course of their disease. The Committee encourages NCI to coordinate its research efforts with the National Center for Complementary and Alternative Medicine. (p.67)

Action taken or to be taken

Collaboration with the National Center for Complementary and Alternative Medicine (NCCAM)

The National Cancer Institute (NCI) and the NCCAM have established a close, collaborative relationship, which has resulted in the establishment of a variety of joint projects.

Cancer Advisory Panel for Complementary and Alternative Medicine (CAPCAM)

The CAPCAM was jointly constructed by the NCCAM and the NCI to (1) review and evaluate summaries of evidence for CAM cancer claims submitted by practitioners, (2) make recommendations to the NCCAM on whether and how these evaluations should be followed up, and (3) be available to observe and provide advice about studies supported by the NCCAM and NCI, and about communication of the results of those studies. The panel's membership is drawn from a broad range of experts from the conventional and CAM cancer research and practice communities. After an organizational meeting held November 16, 1998, the panel was subsequently chartered and is authorized to meet at least twice a year. The first meeting of the chartered panel was held July 8-9, 1999.

The director of the NCI's newly established Office of Cancer Complementary and Alternative Medicine (OCCAM,) is the NCI's liaison to the NCCAM and serves as a member of the CAPCAM. The OCCAM operates the NCI's Best Case Series Program. This program affords opportunities for alternative medicine practitioners to provide information about patients with cancer treated with alternative medical approaches. The medical records and primary source materials (medical imaging studies and pathology specimens) are sent to the OCCAM which checks for completeness of the data, arranges the review of the radiology and pathology, summarizes and presents the materials to the CAPCAM for review.

Oral Shark Cartilage Clinical Trials

Due to public interest in the potential anti-cancer activity of shark cartilage and its continued use despite the lack of definitive clinical evidence of efficacy, the NCI is collaborating with NCCAM to sponsor clinical trials in this area. The University of Texas M.D. Anderson Cancer Center and the North Central Cancer Treatment Group have been selected to perform clinical trials to assess the anticancer activity of two oral shark cartilage products. These trials are expected to begin accrual of patients in early calendar year 2000.

Evaluation of Intensive Pancreatic Proteolytic Enzyme Therapy with Ancillary Nutritional Support in the Treatment of Inoperable Adenocarcinoma

The NCI has provided administrative support to allow the National Center for Complementary and Alternative Medicine (NCCAM) to begin a large prospective evaluation of a nutritional program with oral pancreatic enzymes and a "detoxification" regimen at Columbia Presbyterian Medical Center, one of the NCI designated Cancer Centers. This clinical trial will compare this alternative medicine designed regimen to conventional chemotherapy for patients with advanced pancreatic cancer. The protocol is open to patient accrual and is advertised on the NCI's Physicians Data Query (PDQ).

Request for Applications for Centers for Complementary and Alternative Medicine Research in Cancer

The NCI is participating in a recently released request for applications (RFA) by the NCCAM for proposals for new centers for CAM research. Successful applicants with centers focused on cancer will be jointly supported.

The NCI has also independently initiated other CAM projects that have been strongly supported by the NCCAM.

Green Tea Projects

NCI staff in the Division of Cancer Prevention have been instrumental in establishing phase I and II clinical trial protocols using formulations of the active components from green tea at two major U.S. medical centers.

Establishment of Cancer CAM Research Interest Group

In February 1999, the NCI established the Cancer CAM Research Interest Group. This group is the only continuous and open forum for members of the NIH community to learn about and discuss the current status and potentials of CAM research as relates to the treatment of cancer patients. The group's monthly are open to all the scientific and clinical staff of the NIH and other government agencies.

Meetings of the interest group have been the forum for major lectures on topics such as: Amazonian tribe botanicals and African zoopharmaceuticals, the effects of herbal extracts on animal and human chromosomes, and traditional Indian ayurvedic medicine. These lectures as well as others on the potential preventive effects of nutrition on breast and colorectal cancer provided through the NCI Grand Rounds Series have increased the dialog at NIH about these important CAM and CAM-related issues.

CAM-Related RFAs

The NCI has participated in a number of CAM-related RFAs such one for Botanical Research Centers initiated by the Office of Dietary Supplements and one for Centers for Mind–Body and Health Interactions initiated by the Office of Behavioral and Social Science Research.

Intramural CAM Research

The NCI is also supporting intramural research in CAM and cancer. Two surveys of the use of CAM therapies among patients on phase I clinical trials and by women at high-risk for breast cancer are underway at the NIH Clinical Center and the Bethesda Navy Medical Center. Also a clinical trial of the potential therapeutic role of a soya compound (genistein) in cancer patients is underway.

CAM Information Projects

Revision of the NCI's CAM Information Review Process

The NCI is revising its information on alternative medicine on the CancerNet website. The new statements are reviewed by the appropriate PDQ editorial board as well as ad hoc reviewers with CAM expertise. Summaries of hydrazine sulfate and cartilage products have been completed and others are in production.

OCCAM Website

The NCI's Office of Cancer Complementary and Alternative Medicine is developing an Internet site to communicate with the general public and extramural research and practice communities. This site will give updates of the status of current and planned NCI CAM projects and will serve to help make the NCI's agenda in these areas more accessable.

CAM Cancer Research Citation Database

The NCI will work with the NCCAM to amplify the existing CAM Citation Index which contains information about thousands of scientific articles about the use of CAM in various medical conditions. This database will be accessible from both the NCCAM's website and the OCCAM's website and will be a resource for both the general public and researchers.

Support and Participation in Comprehensive Cancer Care Conferences

In fiscal year 1999 the NCI co-sponsored and substantially participated in a conference designed to bring together the conventional and CAM cancer research and practice communities. NCI staff presented information the NCI's Best Case Series, NCI/NCCAM research projects, funding CAM cancer research and palliative care issues. The NCI will again participate in this conference in June 2000 and will work with the NCCAM to encourage the initiation of other conferences on CAM in cancer.

Office of Cancer Survivorship, NCI

Most recently (October 1999), the Office of Cancer Survivorship (OCS) became responsible for a new Mind/Body Center grant at the University of Miami that will promote psycho-oncology research across the illness and recovery continuum. This application was the result of a trans NIH collaboration, in response to a congressional mandate that included a funding set aside, to establish centers for the Study of Mind Body Interactions and Health. The establishment of this center, responding as it does to the public's growing interest in and use of complementary approaches in cancer care, represents a promising new area of research. All four of the projects proposed under the umbrella of the center include interventions that aim to improve health behaviors (e.g., stress management) and/or quality of life of cancer survivors.

Item

Endometrial Cancer -- While the number of new cases of endometrial cancer remained constant over the last decade, the number of deaths per year from endometrial cancer has more than doubled. Given this two-fold increase, the Committee urges NCI to use all available mechanisms, as appropriate, including holding a workshop to examine research opportunities to identify molecular determinants and markers for this type of cancer. (p.67-68)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. SEER data indicate that cancer of the corpus uteri, or endometrium, is the fourth most common cancer among women in the United States. An estimated 37,400 American women were diagnosed with uterine cancer last year, and over 6,000 American women died from the disease. The age-adjusted incidence rate based on the SEER sampling of approximately 10% of the U.S. population for 1977, 1987, and 1996 are 28.48, 21.55, and 21.06 per 100,000 women, respectively. Thus, the rate of endometrial cancer incidence has fallen by over 26% over the past two decades. The National Center for Health Statistics tracks deaths in the entire U.S. population. The number of deaths due to endometrial cancer was 5,741 in 1977 and rose to 5,894 in 1987 and 6,310 in 1996. Age-adjusted mortality rates in 1977, 1987, and 1996 for the entire U.S. population were 4.26, 3.56, and 3.33 per 100,000, respectively. Thus, even with a falling age-adjusted mortality rate, an increasing population and the aging of our population has resulted in a higher number of deaths for endometrial cancer. The increase in the number of cases registered by SEER from 1987 to 1996 (+10.6%) and the increase in the number of deaths recorded by NCHS (+7.1%) would not indicate that this period has seen an increase in deaths from endometrial cancer that is out of proportion to the increase in cases.

Aging of the U.S. population and of other major industrial nations is a trend that continues to reshape our global demographic, social, economic, political, and cultural structures. Longer life spans, dramatic changes in disease patterns, and the ongoing revolution in biotechnology are reshaping health-related perspectives. Within this broader context and coupled with simultaneous changes in the racial and ethnic composition of our populations, national trends in the U.S. cancer burden are in flux.

Many times it is difficult to understand the inter-relationships of the burden of the disease on a population and the risk of having/dying of a disease. Cancer is predominantly a disease of older Americans with 60 percent of all diagnosed cases and 70 percent of all cancer deaths occurring among persons 65 years and older. The median age at cancer diagnosis is 68 years of age and at 71 years of age for cancer death. A recent article showed that between 1990 and 1996, cancer incidence rates decreased an average of about 1 percent per year and mortality decreased an average of 0.6 percent per year. While the rates have decreased, the trends in number of cancer cases is more unpredictable, and the number of cancer deaths has increased because there are more people in the United States and the population is aging. The racial and ethnic diversity of endometrial cancer follows a pattern similar to that of breast cancer. Women with the highest age-adjusted incidence of endometrial cancer in the SEER areas include Hawaiians, whites, Japanese and blacks. The lowest rates occur among Korean, Vietnamese, and American Indian women.

When the overall U.S. cancer mortality rate for cancers is compared between 1997 and 1990, there was a decline of 5.6 percent while the numbers of deaths increased 6.8 percent due to the population increasing 7.3 percent and the aging of the population. The under 65 age group increased 7.0 percent while the 65+ age group increased 9.5 percent. The declines in cancer mortality were larger in the younger age groups. Overall, the cancer mortality rate declined 11.5 percent for those under 65 in contrast to declining 1.8 percent for those 65 years of age and older. The SEER cancer incidence patterns for the period 1990-1996 varied by sex and age at diagnosis. The largest annual decreases in incidence rates for all sites combined occurred in males who were 25-44 years old and males who were 75 years old and older at diagnosis. Age-specific trends in females were less remarkable, with the only significant decline among those 35-44 years old. Demographers have projected that the population will continue to increase and to age. Between 1997 and 2010, the population will increase 11.2 percent; the <65 age group will increase 10.6 percent and the 65+ age group will increase 15.2 percent. Unless there are really steep declines in the cancer incidence and mortality rates, this means that we will continue to see increases in the overall numbers of cases and deaths. This also means that cancer will continue to be an increasing burden on our health care systems for the foreseeable future.

For the period 1973 to 1996, there has been an approximately 27% decrease in the age-adjusted incidence rates for cancers of the corpus and uterus among all races combined. This decrease coresponds to an average annual percentage decrease of about 1.7% over this period. A statistically significant decrease in the estimated annual percentage change in incidence rates has been seen in all individually monitored racial and ethnic groups with the exception of black women where the incidence rates have increased some 12% over the 1973 to 1996 period. Endometrial cancer, like many cancers, increases with advancing age in most, but not all, racial/ethnic groups. Exceptions to this general pattern are Chinese and Filipino women, among whom the highest rates occur at ages 55-69 years. In younger women, ages 30-54 at diagnosis, endometrial cancer is most common among Hawaiians, Japanese, and whites. At ages 55-69 years, endometrial cancer rates are highest for white, Hawaiian, and black women. At ages 70 years and older, rates are highest among white, black, and Japanese women. There were too few cases in Hawaiian women ages 70 years and older to calculate a rate.

Age-adjusted mortality rates in the United States for endometrial cancer are highest among Hawaiian women, followed by black women. Mortality among white, Hispanic, Chinese, Japanese and Filipino women is less than one-half the rate for Hawaiian women. Age-specific mortality is highest among black women in each of the three age groups (there were too few deaths among Hawaiian women to calculate rates by age). The ratio of incidence to mortality for black women is slightly over two and for Hawaiian women it is nearly three. Chinese women have incidence rates about five times higher than mortality, for white women the ratio is seven, for Japanese women it is nearly eight, and for Filipino women it is about nine. The smaller incidence-to-mortality ratios among black and Hawaiian women suggest that access to care may be a more acute problem for them.

Several issues contribute to making endometrial cancer a high priority for the Institute. These include: the use of hormone replacement therapy to treat the symptoms of menapours, use of tamoxifen in breast cancer treatement and chemoprevention, and the increasing rate of obesity in American womem. Endometrial cancer has also been associated with diabetes, cigarette smoking, and physical activity but possible mechanisms remain obscure. The predominant risk factor for this cancer is the use of exogenous menopausal estrogens. When menopausal estrogens are taken with progesterone, the elevation in risk is greatly reduced. Tamoxifen, a drug that is widely used to treat breast cancer and in prevention for individuals at higher risk of breast cancer, appears to have estrogen-like effects on the uterus, and may also be associated with increased risk of endometrial cancer. Excepting these risk factors, the epidemiology of endometrial cancer is not well defined.

The NCI is supporting research on endometrial cancer through a variety of support activities. The NCI-sponsored Clinical Trials Cooperative Groups, particularly the Gynecologic Oncology Group, continue to work to develop more effective therapy for women with endometrial cancer. NCI is currently sponsoring over 100 clinical trials for endometrial cancer, including five Phase III trials. These phase III trials are testing those treatments closest to clinical practice. Through the Gynecologic Cancer Intergroup, timely completion of phase III trials will help to identify active treatments in this disease. In addition, the NCI plans a workshop on translational research in gynecologic cancer, to be held in May 2000, which will address issues of molecular determinants and markers in endometrial, cervical, and ovarian cancer.

In addition to the research through the groups mechanism, NCI is funding a variety of single investigators whose research is also focused upon aspects of endometrial cancer. Efforts are underway to better understand the pathogenesis and progression of both sporadic and hereditary endometrial cancers through the analysis of genetic alterations. Roughly 20% of endometrial cancers have a defect in DNA mismatch repair. Defects in DNA mismatch repair lead to genome-wide instability of microsatellite repeats and a molecular phenotype called microsatellite instability. This phenotype has been shown to be consistently present in tumors from patients with hereditary nonpolyposis colorectal cancer (HNPCC). Endometrial cancers are the second most common tumors in these families. It was recently reported that methylation of the MLH1 promoter and gene silencing is the primary cause of microsatellite instability in endometrial tumors. The results of preliminary studies of the expression of the MSH2 DNA mismatch repair gene in endometrial cancers provide additional evidence that this gene may be important in inherited forms of this disease. There was also a recent evaluation of microsatellite instability

and mutations of the gene PTEN in complex atypical hyperplasia (CAH), the precursor to endometrial carcinoma. The results of these studies suggest that mutation of PTEN is an early event in the pathogenesis of endometrial cancer and may precede the development of microsatellite instability in a subset of cases. Although these preliminary indications are promising, additional study is needed to further define the role of genetic alterations in the development of endometrial cancers and to determine whether these markers can be used to predict risk in families with the hereditary form of this disease.

NCI is also supporting efforts to isolate a novel tumor suppressor gene which is involved in the development of uterine papillary serous carcinoma (UPSC), the most aggressive type of endometrial cancer. The research has identified a del(1p32-33) in approximately 65% of USPCs and has now narrowed the endometrial cancer deletion region at 1p32-33 to less than one cM region. Cloning the gene involved in the deletion should contribute to an understanding of the mechanism of endometrial cancer development and provide a marker to evaluate whether the involvement of the 1p tumor suppressor gene contributes to poor prognosis.

NCI is also supporting investigator initiated research to elucidate the mechanism(s) by which antiestrogens act and elicit differential effects on the breast and the uterus. There are two critical questions each highly clinically relevant. (1) What are the molecular mechanisms that can explain as to why patients fail antiestrogens therapy, or more specifically what is the explanation for tamoxifen-resistance in breast tumors? (2) What are the molecular mechanisms, which can explain dual effects of tamoxifen or other antiestrogens: as antiestrogens in the breast and as an estrogen on the uterus.

One area of research is trying to define unique nuclear proteins (transcription factors) in the uterine tissues, which can explain the “estrogenicity” of tamoxifen in the uterus. Once identified, she can then elucidate how these specific nuclear factors affect tamoxifen-bound activation of estrogen receptors resulting in the stimulation of uterine growth.

Another focus of study is elucidating pathways by which estrogen receptors activate cell signal transduction pathways from the cell surface to the nucleus in normal and malignant uterine tissues. This research has already identified a unique protein (MEKK1), which increases estrogen receptor activity but only in endometrial and endometrioid type of tumors. More important, the estrogenic activity of tamoxifen is significantly increased in the presence of MEKK1.

A third area of research is interested in the mechanism by which tumors become refractory to tamoxifen therapy. This study has showed that an important regulatory protein, Protein Kinase C (PKC) is overexpressed in breast and endometrial cells. In the presence of PKC tamoxifen can act as estrogen and promote growth of breast and Endometrial cancer cells.

These investigations will aid in elucidating the mechanism of tamoxifen-stimulated breast and endometrial cancers and will identify possible targets for treatment. If the mechanism(s), which result in the “estrogenic” effect of tamoxifen, are clearly delineated, it would allow the development of more effective antiestrogenic therapy.

NCI supported investigators are also conducting a study of women taking tamoxifen to test the hypothesis that women who develop atypocal endometrial growth or cancer in response to tamoxifen do so because their endometrial cells contain relatively high levels of the B form of the preogesterone receptor, which under the influence of progesterone, stimulates the production of the enzyme flavin-containing monoxygenase 5.

Estrogens are a major risk factor for hormone-dependent endometrial and breast cancers in women. A number of genes are regulated by the alpha and beta forms of the estrogen receptor (ER) protein, usually through direct interaction with DNA at specific sites in the target genes. However, in exploring estrogen regulation of several genes whose expression is important in cancer, it has been discovered that estrogen can induce gene expression through mechanisms that do not include direct binding of the ER to DNA. Instead, the estrogen-bound ER cooperates as a coactivator with several other proteins that are ubiquitous gene regulators and whose activity is controlled by several major cell signaling pathways. It is crucial to unravel these numerous interactions because they may be responsible for the development of resistance to chemotherapy.

In 1992, the NCI established the Specialized Programs of Research Excellence (SPOREs) to promote interdisciplinary research and to speed the bidirectional exchange between basic and clinical science to move basic research finding from the laboratory to applied settings involving patients and populations. The goal of the SPORE program is to bring to clinical care settings novel ideas that have the potential to reduce cancer incidence an mortality, improve survival, and to improve the quality of life. Laboratory and clinical scientists work collaboratively to plan, design and implement research programs that impact on cancer prevention, detection, diagnosis, treatment and control. To facilitate this research, each SPORE develops and maintains specialized resources that benefit all scientist working on the specific cancer cite, as well as SPORE scientists. An additional SPORE element is a career development program that recruits scientists both within and outside the SPORE institution to enlarge the cadre of laboratory and clinical scientists dedicated to translational research on human cancer. SPOREs meet annually to share data, assess research progress, identify new research opportunities and establish priorities for research most likely to reduce incidence and mortality and to increase survival. In 1998, NCI funded a total of 14 SPORES and co-funded 6 SPORES for a total of $30 million. SPORES are funded through specialized center grants (P50s).

In the upcoming years, NCI will increase the use of the SPORE mechanism to include funding for other major cancer sites. A SPORE conducts translational research that requires interdependence between basic and clinical investigators in both the planning and implementation of research and emphasizes the application of basic research findings to patients and populations. Based on NCI's projections regarding the growth of the SPORE program, it is anticipated that applications for a SPORE focused on gynocologic cancers will occur in 2003.

In part to assist researchers in institutions considering the development of an application for a Gyn SPORE, the NCI will be sponsoring a retreat in May of 2000 meant to foster translational research on gynecologic cancers. This retreat will focus on epithelial ovarian cancer, endometrial cancer, and HPV-associated cancers of the cervix, vagina, and vulva.

The NCI also intends to establish a Progress Review Group (PRG) early in fiscal year 2001 to assist in setting priorities for research on gynocological cancers including endometrial cancer. Like other PRGs, this PRG will be composed of between 21 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research. The final product of the PRG will be a report listing research priorities and discussing the extent to which these priorities are being met. NCI will issue this report in mid-fiscal year 2002.

Item

Gastrointestinal Cancers -- Gastrointestinal cancers include colorectal cancer, lower esophageal and upper stomach cancers, pancreatic cancer, liver/intrahepatic bile duct cancer, and gallbladder and other biliary cancers. The Committee urges NCI to enhance its efforts in these areas with particular focus on the genetic aspects of gastrointestinal cancer, diagnostic tests for genetic abnormalities and prevention, and environmental factors relating to the development of this disease. The Committee also urges NCI to enhance its efforts in the development and treatment of Barrett's syndrome, a precursor to lower esophageal and upper stomach cancer, in patients with gastroesophageal reflux disease. (p. 68)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Cancers of the digestive system claimed 131,000 American lives last year with 226,300 new cases diagnosed. The largest number of these new cases (129,400) and deaths (56,600) were associated with colorectal cancer. Other leading gastrointestinal cancers include: pancreatic cancer (28,600 new cases and 28,600 deaths); stomach cancer (21,900 new cases and 13,500 deaths; liver and intrahepatic bile duct cancer (14,500 new cases and 13,600 deaths); and esophageal cancer (12,500 new cases and 12,200 deaths)

Colorectal Cancer

Colorectal cancer is the third most common cancer in both men and women with about 130,000 new cases each year. Although incidence rates have been declining by about 1.4% per year since 1991, nonetheless cancers of the colon and rectum are the second leading cause of cancer death in the United States claiming about 56,000 lives in 1999. When colorectal cancers are detected in an early, localized stage, 5-year relative survival rates are over 90%. However less than half of colorectal cancers are discovered at this stage and the survival rate for persons with distant metastases at diagnosis is under 10%.

The NCI has an extensive research portfolio in colorectal cancer with about $130 million expended in 1999 which supports over 300 separate research grants related to colorectal cancer. The level of NCI's support for research on colorectal cancer site doubled in just the last decade, a rate of increase that exceeds the increase in the overall NCI budget during this time frame.

Even with this large ongoing effort, the NCI recognizes that more must be done to combat colorectal cancer. Accordingly, he NCI Director has convened a Colorectal Cancer Progress Review Group (CPRG) in the fall of 1999 to sharpen the focus of its large, site-specific research programs with respect to colorectal cancer. The overall goal of the CPRG is to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities which will need to be addressed in order to make progress in understanding, treating, and ultimately preventing colorectal cancer.

The CPRG will meet two to three times to assess NCI's current colorectal cancer portfolio, review input from outside experts, gather additional data, prioritize key scientific questions, and develop recommendations for action. In addition, a PRG "Roundtable" will be convened in January 2000 to include over 150 leading members of the colorectal cancer research and advocacy communities. The Roundtable participants meet in an open forum designed to formulate key scientific questions for the next five to ten years in colorectal cancer research and to inform the deliberations of the CPRG.

The specific charge given the CPRG was to:

- Identify and prioritize scientific needs and opportunities that are critical to hastening progress against colorectal cancer.
- Review an NCI-prepared portfolio analysis of the current research program.
- Review recommendations from the research community generated through the Colorectal Cancer Roundtable meeting.
- Define and prioritize the research agenda.
- Develop an action plan encompassing both operational and strategic components of the NCI's colorectal cancer enterprise, using the current research program as the baseline for recommended actions.

Members of the CPRG, representing basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community are working together to develop a broad, multidisciplinary perspective of ongoing colorectal cancer research. This group of experts, using input from the scientific community and a comprehensive report of the NCI's colorectal cancer research portfolio will identify and prioritize scientific needs and opportunities critical to advancing the field in the next five to ten years. In addition to the CPRG, the NCI funded cooperative groups will hold an intergroup state of the science meeting on colorectal cancer, which will address translation of basic research to clinical usefulness in February 2000.

Molecular Biology/Molecular Diagnosis/Genetics

In the past, translation of discovery of new molecular markers for the earliest stages of cancer development into useful early detection and screening tests has been impacted by lack of a direct linkage between the basic "discovery" laboratories with expertise in quality control for clinical tests, and clinical groups with access to appropriate patient populations. Recognizable the need for a "vertical integration" of the science in each of these areas, the NCI has recently formed a cooperative consortium designed to develop and prioritize molecular early detection markers for

human studies. Colorectal cancers are an area of special emphasis in this Early Detection Research Network (EDRN).

In October 1999, the NCI awarded Biomarker Developmental Laboratory grants to 18 awardees, through the Early Detection Research Network. These laboratories will perform the basic genetic and protein biomarker analyses which are intended to improve detection of malignancy. Five of these studies will focus in part on colorectal cancer. Projects with direct relevance to colorectal cancer include:

- Analysis of genes involved in colon cancer and identification of mutations involved in early cancer formation.
- Assessment of patterns of expressed colon cancer related proteins.
- Analysis of blood for markers of early colon cancer.
- Analysis of stool samples for shed cellular products of colorectal cancer

In 2000, the two remaining major components of the EDRN will be funded: Biomarker Validation Laboratories for standardization and lab validation of biomarker measurements; and five Clinical Epidemiology Centers for pilot phase testing in people with cancer and at high risk of cancer. There will also be a funded Data Management Center.

One project funded through the Directors' Challenge this year will develop molecular profiles for stage II and III colon cancer to identify patients at highest risk of developing metastatic disease after potentially curative surgery. Several investigator initiated grants were funded from the Cancer Diagnosis Program, as well as the Cancer Therapy Evaluation Program which seek to define molecular abnormalities associated with the development, progression or treatment response of colorectal cancer. These studies of molecular, genetic and protein expression in colorectal cancer will provide information which may lead to diagnositic tests available for the general population. Sponsored Programs for Research Excellence (SPOREs) in Gastrointestinal cancer, of which there are two, will concentrate their research on the translation of molecular insights into clinical benefit.

Screening

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, begun in 1991, and continuing for 16 years, will compare colorectal cancer screening by flexible sigmoidoscopy vs. usual care with the screened group being composed of 37,000 men and 37,000 women. Serum, whole blood and buffy coat (a source of DNA) are being archived for each individual screened in each of the first 3 years of the trial. These materials will be an important resource for studies of future candidate markers of early detection and/or risk.

Report to the Nation

Work is underway to develop the 2000 Report to the Nation, a collaborative effort to provide the latest information on cancer incidence and death rates, with an emphasis this year on what is known about colorectal cancer. The report will publish cancer incidence rates for 1973-1997 based on data from the NCI SEER Program, which covers approximately 14% of the U.S.

population, and cancer death rates through 1997 that are reported by the National Center for Health Statistics [NCHS] for all states and the District of Columbia. In addition, the report will examine in detail cancer rates during the 1990s for men and women, blacks and whites, and the major cancer sites. Selected information will be reported for other racial and ethnic populations, as well as for the top ten cancers, including colorectal cancer and death rates for cancer of the pancreas and stomach. A new statistical technique, called joinpoint regression, has been applied to these data to investigate more closely the changes in cancer trends for specific groups. Substantial data on colorectal cancer incidence and death rates, along with survey data from the state-based Behavioral Risk Factor Surveillance System [BRFSS] reported by the Centers for Disease Control and Prevention [CDC], are featured. Of interest are BRFSS data on screening patterns specific to colorectal cancer, i.e., the annual fecal occult blood test and/or periodic flexible sigmoidoscopy for persons ages 50 and older, that reduce colorectal cancer-related mortality. These data are discussed in the context of SEER colorectal cancer trends based on the anatomic area of the colon and rectum in which the cancer occurred. Lastly, the annual report will include state-specific cancer incidence data from high quality cancer registries funded by the CDC National Program of Cancer Registries [NPCR] and prepared under the auspices of the North American Association of Central Cancer Registries [NAACCR]. The American Cancer Society is another key member of this collaborative public-private enterprise.

Modifiable Risk Factors - Projecting Trends

Trends in risk factors for colon cancer (vegetable intake, red meat intake, alcohol consumption, physical activity levels, and weight status) were modeled for the U.S. adult population over the years 1975 to 1995, in an effort to explain the decline in colon cancer incidence from 1985 to 1995. Increased vegetable intake and decreased intakes of red meat and alcohol reduced risk, while reduced physical activity and increased body mass index increased risk for colon cancer. When all five factors were considered together, change in the average population risk was small and the risk factors accounted for very little of the recently observed decline in incidence.

Colorectal Cancer Surveillance Consortium

A number of small pilot studies are ongoing to provide information on potential methods and organizational structure for data collection. A concept for a RFA/cooperative agreement is in initial stages of conceptualization and a working meeting of expert consultants will be held in March 2000 to help NCI develop this concept further.

Physician / Health Plan Surveys

In keeping with its mission, the Applied Research Program of the Division of Cancer Control and Population Sciences, tracks the use of screening modalities, therapies, new technologies, and other factors that may influence the cancer burden nationally. Applied Research Program activities include two studies, the Physician Survey on Cancer Susceptibility Testing and the Survey of Colorectal Cancer Screening Practices in Health Care Organizations, are currently underway.

Physician Survey on Cancer Susceptibility Testing

There is currently no information available for assessing the prevalence of genetic testing for cancer susceptibility genes at the national level, or for evaluating the knowledge of and attitudes toward such testing among physicians. ARP has initiated a national survey, mainly among physicians in the primary care specialties, that is designed to ascertain baseline information about use, knowledge of, and attitudes towards the new technology of genetic tests for inherited cancer susceptibility. The study sample will consist of approximately 1350 physicians, including 900 primary care physicians (e.g., general internists, gynecologists, family, and general practitioners) and a comparison group of 450 specialists who treat cancer patients and individuals at high risk for cancer (e.g., gastroenterologists, surgeons, urologists and oncologists).

Survey of Colorectal Cancer Screening Practices in Health Care Organizations

This study will obtain current, nationally representative data on the physician and health system factors that may influence the use of screening and diagnostic follow-up for the early detection of colorectal cancer in community practice. Study participants are primary care physicians who are likely to administer colorectal cancer screening tests to adult patients or to refer patients to specialty physicians for such tests; specialty physicians who are likely to conduct colorectal cancer screening as well as diagnostic follow-up and surveillance procedures for suspected colorectal cancer; and health plan medical directors. Questionnaires will be administered by mail, telephone, facsimile, or Internet using randomly-drawn national samples of physicians (n = 1,059 primary care and n = 1,042 specialty) and health plans (n = 323). Study participants will select their preferred response mode.

MISCAN Project

MISCAN-COLON is a microsimulation modeling program designed to evaluate the costs and health effects associated with various strategies of colorectal cancer screening. MISCAN-COLON was produced by the Department of Public Health, Erasmus University, under an NCI contract. The model is currently being refined through a variety of validation studies and being used to aid several policy analyses in the U.S., Canada and Europe.

SEER-MEDICARE

The SEER-Medicare (SEER = Surveillance, Epidemiology, and End Results) database is the collaborative effort of the National Cancer Institute (NCI), the SEER registries and the Health Care Financing Administration (HCFA) to create a large population-based source of information for cancer related epidemiologic and health services research. Current SEER-Medicare projects related to colorectal cancer include studies of the treatment cost of colorectal cancer, studies of treatment patterns and survival by type of medical provider, fee-for-service or HMO, use the Medicare hospice benefit by patients with colorectal cancer and a population-based analysis of serious toxicity outcomes following therapy for colorectal cancer and the costs of treatment for chemotherapy for metastatic colorectal cancer.

Cancer Intervention and Surveillance Modeling Network (CISNET)

In the past, most models of cancer interventions (i.e., treatment, screening, primary prevention) have been developed to describe hypothetical cohorts in a trial or other limited clinical settings. This initiative will promote the development of models to describe the population impact of these interventions. Projects can focus on models describing: (1) the population dissemination of new interventions, (2) the impact of interventions on observed national trends, (3) the potential impact of new interventions on future national trends, and/or (4) determining the impact of targeted cancer control interventions on population outcome. The first round of funding will focus on prostate, breast, and colorectal cancers. The cooperative agreement RFA mechanism will allow the development of site-specific working groups which will: (1) facilitate comparative analyses, (2) allow modeling groups access to a broader array of data resources and multidisciplinary expertise, and (3) provide a forum for discussions of validation and other methodologic issues. The goal of this research is to help: (1) answer the "why" questions in the analysis of cancer incidence and mortality trends, (2) determine if recommended interventions are having their expected population impact, and (3) predict the potential of new interventions on national trends. Over 30 grant applications where received in November 1999 for the initial issuance of the CISNET RFA. The first round of funding in fiscal year 2000 is for projects related to colorectal cancer, breast cancer and prostate cancer.

Cancer Genetics Network

The CGN is a multi-center, interdisciplinary consortium that serves as a an infrastructure for the design and implementation of individual research projects in basic cancer genetics, genetic epidemiology, clinical and behavioral issues related to genetic risk, cancer preventive strategies for groups at genetic risk, and other public health implications of predictive genetic testing. The Network currently comprises eight participating centers with active programs in predictive genetic testing for cancer risk and established excellence in basic human genome research. These include Duke University, Georgetown University, Johns Hopkins University, the University of Pennsylvania, the University of Texas (M.D. Anderson Cancer Center), the University of California (Irvine), and the University of Washington (Fred Hutchinson Cancer Research Center). The Centers are linked to form a single virtual center by a state-of-the-art informatics system (the Informatics and Technology Group (ITG)) that transfers information and channels specimens using the latest information technology approaches. A pilot study has been approved and is, or soon will be, under implementation at multiple centers: “Recruitment of Sib Pairs with Colon Cancer for Gene Discovery Studies (in collaboration with the Cancer Family Registries for Colon Cancer).”

Cancer Family Registry

The Cancer Family Registry for colorectal studies (CFR) is a collaborative research infrastructure progressively established by the National Cancer Institute to facilitate interdisciplinary studies in the genetics and epidemiology of cancer. The institutions participating in this international initiative have committed themselves to collect family history information, epidemiological and clinical data, and biological specimens from individuals and patients with a family history of colon cancer ascertained from a variety of populations within

and outside the United States. The CFR is particularly geared to support the identification of novel cancer susceptibility genes. Further, the CFR infrastructure will make possible the characterization of the colorectal cancer susceptibility genes that have already been identified in terms of their penetrance and distribution in the general population, the correlation between genotype and phenotype in these forms of cancer, and the effect of modifier genes, environmental exposures and/or lifestyle factors (such as diet, physical activity and hormonal exposure) on cancer risk. In addition, the prospective follow-up of the CFR cohort and the systematic collection of clinical and pathological data will provide important information on survival, morbidity and mortality in a population at high risk for cancer, with the possibility of immediate application in the design and choice of appropriate preventive and therapeutic strategies. The six awardee institutions for the colorectal cancer CFR, University of Southern California, University of Hawaii, Mayo Foundation, Fred Hutchinson Cancer Research Center, Cancer Care (Toronto, Canada), and the University of Queensland (Australia) are now recruiting and proceeding with the molecular characterization of the participating families.

Prevention

The ongoing Women's Health Initiative is a prevention study of diet, Vitamin D, calcium, and hormones with respect to colorectal cancer.

Phase III placebo-controlled, randomized trials for the prevention of large bowel polyps are ongoing. One trial randomizes patients with a history of bowel adenoma to 2 different doses of aspirin and folic acid, vs. placebo. A second trial randomizes similar patients to wheat bran fiber vs. calcium carbonate. A third phase III randomized placebo controlled double blind study of celecoxib is ongoing for patients with sporadic adenomatous polyps. A fourth trial randomizes patients with a history of adenomas to alpha-difluoromethylornithine (DFMO) $\pm$ Sulindac.

Several phase II trials in adenomas, the precursor to colorectal cancer, are being carried out. These trials assess the activity of various putative chemopreventive agents (e.g., Calcium and Vitamin D, Folic acid, Aspirin, Piroxicam, Sulindac, Celecoxib, DFMO, phenolic compounds, polyamine depletion, and diet) in preventing polyp formation or progression. The effect of the chemopreventive agent on various biomarkers, such as proliferative index, apoptotic index, Cyclooxygenase-2 (COX-2) expression, and genetic abnormalities are also being assessed.

Through their Division of Cancer Prevention's Community Clinical Oncology Program (CCOP) Research Base Grants, each of the multispecialty Cancer Cooperative Groups has activated a colorectal cancer prevention trial: Southwest Oncology Group (SWOG) 9041 randomized 200 patients with either adenomas or stage I or II colorectal cancer to calcium supplementation or placebo for 5 years. The study closed in April 1999, and is awaiting maturation and analysis. Cancer and Leukemia Group B (CALGB) has an open trial that is randomizing patients with adenomas to aspirin or placebo. Eastern Cooperative Oncology Group (ECOG) has a small biomarker study that randomizes patients with colonic adenomas to folic acid or placebo. In addition, the large, randomized trials of adjuvant treatment being carried out in the Cooperative Group system will collect tissue for analysis of genetic and other biomarker data. It is hoped that these data will allow physicians to predict which patients will benefit from adjuvant therapy, and, just as important, which patients may not need adjuvant therapy.

The intramural Medicine Branch in the NCI has established a "Genetics Department," which participates in the Cancer Genome Anatomy Project and also has a clinical cancer genetics program, focused on the genetics of colorectal and breast cancer. For colorectal cancer, this program, run jointly with NHGRI, focuses on education and counseling for individuals at increased risk for the development of colorectal cancer because of family history or age at diagnosis of the index case, accompanied by evidence of a particular molecular pathway associated with colorectal carcinogenesis. Following the education and counseling study, participants are given the opportunity to participate in a germline testing process. Depending on the findings in this process, individuals may be eligible to participate in a selective COX-2 inhibitor chemoprevention protocol, during which biomarkers in colonic mucosa are assessed periodically.

Pancreatic Cancer

An estimated 28,600 new cases of pancreatic cancer were diagnosed in the United States in 1999. Although the incidence rates of pancreatic cancer in men have declined over the past 20 years, the incidence rates in women have remained approximately constant. Similarly while death rates in men have decreased by about 1% per year lately, the mortality rate from pancreatic cancer in women has increased slightly. The NCI expended approximately $15.5 million in fiscal year 1999 on pancreatic cancer and supports over 100 research grants related to pancreatic cancer. Even with this ongoing effort the NCI is desirous of funding more research on pancreatic cancer. To set priorities for this research, the NCI Director is convening a Pancreatic Cancer Progress Review Group (PaCPRG) in the Spring of 2000 to sharpen the focus of its large, site-specific research programs with respect to pancreatic cancer. The overall goal of the PaCPRG is to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities which will need to be addressed in order to make progress in understanding, treating, and ultimately preventing pancreatic cancer.

Several investigator initiated studies have been funded, which study genetic predispositions to cancer (such as the tumor suppressor gene DPC4, a target of 18Q homozygous deletions, which are present in 90% of pancreatic cancers, and the mucin MUC4), as well as discovery of secreted proteins, which may be diagnostic of pancreatic cancer. SPOREs are concentrating on finding new genetic markers for pancreatic cancer. The Biomarker Developmental Laboratory grants from the Early Detection Research Network funded a laboratory which will perform detailed mutational analysis of specific genes using a variety of technologies, and develop new technologies which can quantify point mutations at the cytologic level in pancreatic fluids.

In previous solicitations for gastrointestinal SPOREs in 1992 and 1996, NCI requested that at least one project of the SPORE should be in pancreatic cancer. Two SPOREs were funded in the second solicitation and one of them, from the University of Nebraska was entirely focused on pancreatic cancer. For the other funded SPORE (Johns Hopkins University), 50% of the research is dedicated to pancreatic cancer. Together, these two projects represent about $3.5 million total costs dedicated to pancreatic cancer research. Both SPOREs have significant developmental therapies and early diagnosis and detection research activities.

Treatment of Pancreatic Cancer

In addition to surgery, three types of treatment are most commonly used in cancer treatment:

- Radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells and shrink tumors)
- Chemotherapy (using drugs to kill cancer cells and shrink tumors)
- Immunotherapy (treating cancers with antibodies or therapeutic vaccines)

All three of these approaches are being used in NCI-sponsored clinical trials for patients with pancreatic cancer. The NCI's PDQ database contains over 180 trials open to patients with pancreatic cancer. Of these, 125 are NCI-sponsored including 94 Phase I trials in which new interventions are being tested for safety and 5 Phase III trials representing treatments that are closest to introduction into general medical practice.

Drugs used in chemotherapy use different ways to stop tumor cells from dividing so they stop growing or die. Radiation therapy uses high-energy x-rays to damage tumor cells. Combining radiation therapy with chemotherapy may kill more tumor cells. It is not yet known which treatment regimen is most effective for pancreatic cancer. One NCI-sponsored randomized phase III trial seeks to compare the effectiveness of fluorouracil and gemcitabine plus radiation therapy in treating patients with cancer of the pancreas who have undergone surgery.

Surgery to remove the pancreas, some of the small intestine, and lymph nodes may be more effective treatment for cancer of the pancreas than surgery to remove the pancreas and some of the small intestine alone. Combining surgery, radiation therapy, and chemotherapy may be an effective treatment for cancer of the pancreas. Another NCI-Sponsored randomized phase III trial aims to compare the effectiveness of surgery to remove the pancreas and a portion of the small intestine with or without removing lymph nodes, followed by radiation therapy and chemotherapy, in treating patients with cancer of the pancreas.

With the approval of a second "active" drug in pancreatic cancer, interest in new drugs for clinical trial in this disease has increased. Determination of the overexpression of ras and the realization that the protein resulting from the expression of this gene must be modifed by farnesylation before it can perform its function has led to interest in drugs which inhibit farnesylation. These are beginning to enter clinical trials in pancreatic cancer. Trials of this nature, when supported by NCI, are usually accompanied by some assessment that the target has been affected, in tissue. It is hoped, in this way, to discover a biologically effective dose (drug inhibits the target) and not have to rely on toxicity to determine an effective dose for clinical trials of the drug's efficacy against a certain tumor.

The NCI has provided administrative support to allow the National Center for Complementary and Alternative Medicine (NCCAM) to begin a large prospective evaluation of a nutritional program with oral pancreatic enzymes and a "detoxification" regimen at Columbia Presbyterian Medical Center, one of the NCI designated Cancer Centers. This clinical trial will compare this alternative medicine designed regimen to conventional chemotherapy for patients with advanced

pancreatic cancer. The protocol is open to patient accrual and is advertised on the NCI's Physicians Data Query (PDQ).

The NCI is in preparation to build a long-range plan for pancreatic cancer research and education efforts. The NCI Director previously scheduled and will convene a Pancreatic Cancer Progress Review Group (PaCPRG) in the Spring of 2000 to sharpen the focus of NCI's large, site-specific research programs with respect to pancreatic cancer. The overall goal of the PaCPRG is to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities that will need to be addressed in order to make progress in understanding, treating, and ultimately preventing pancreatic cancer. The PaCPRG will likely submit its final report at the end of the year 2000 with the subsequent NCI response to the PRG report expected in the Spring of 2001.

The PaCPRG will meet two to three times to assess NCI's current pancreatic cancer portfolio, review input from outside experts, gather additional data, prioritize key scientific questions, and develop recommendations for action. In addition, a PRG "Roundtable" will be convened in the Fall of 2000 to include over 150 leading members of the pancreatic cancer research and advocacy communities. The Roundtable participants meet in an open forum designed to formulate key scientific questions for the next five to ten years in pancreatic cancer research and to inform, expand and focus the deliberations of the PaCPRG. The specific charge to be given to the PaCPRG is to:

- Identify and prioritize scientific needs and opportunities that are critical to hastening progress against pancreatic cancer.
- Review an NCI-prepared portfolio analysis of the current research program.
- Review recommendations from the research community generated through the Pancreatic Cancer Roundtable meeting.
- Define and prioritize the research agenda.
- Develop an action plan encompassing both operational and strategic components of the NCI's pancreatic cancer enterprise, using the current research program as the baseline for recommended actions.

Members of the PaCPRG, representing basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community will work together to develop a broad, multidisciplinary perspective of ongoing pancreatic cancer research. This group of experts, using input from the scientific community and a comprehensive report of the NCI's pancreatic cancer research portfolio, will identify and prioritize scientific needs and opportunities critical to advancing the field in the next five to ten years.

Esophageal and Stomach Cancers

Esophageal and stomach cancers combined account for more than 34,000 new cases in the U.S. Each year and over 25,000 annual deaths. The NCI funds 32 research projects related to esophgeal cancer and 35 research projects related to stomach cancer. The incidence of esophageal cancer has risen in recent decades, coinciding with a shift in histologic type and primary tumor location. Adenocarcinoma of the esophagus is now more prevalent than

squamous cell carcinoma in the United States and western Europe, with most tumors located in the distal esophagus. The cause for the rising incidence and demographic alterations is unknown. While risk factors for squamous cell carcinoma of the esophagus have been identified (tobacco, alcohol, diet, etc.), the risk factors associated with esophageal adenocarcinoma are less clear. The presence of Barrett's esophagus is associated with an increased risk of developing adenocarcinoma of the esophagus, and chronic reflux is considered the predominate cause of Barrett's metaplasia. The results of a population-based, case-controlled study from Sweden strongly suggest that symptomatic gastroesophageal reflux is a risk factor for esophageal adenocarcinoma. The frequency, severity, and duration of reflux symptoms were positively correlated with increased risk of esophageal adenocarcinoma.
The incidence of adenocarcinoma of the lower esophagus and stomach has been increasing since the 1970s, so that now, adenocarcinoma, rather than squamous carcinoma, represents the majority of cancers diagnosed at this site in the U.S. This is an area of intense interest for treatment trials in the NCI funded cooperative groups and cancer centers, with new drugs which are potentially effective alone and in combination with radiation therapy. In addition, newer modalities, such as photodynamic therapy, are being evaluated.

Several investigator initiated grants have been funded which focus on epidemiology and risk factors (i.e., smoking, diet, use of histamine #2 receptor antagonists for gastroesophageal reflux), as well as on molecular markers which may be associated with progression from Barrett's esophagus to cancer (which will only occur in about 10% of patients. One of these is a study of the mechanisms of human esophageal carcinogenesis in Henan Province of Northern China (an area of high incidence of esophageal cancer). Another investigator initiated study will scan the genome for amplified genes in esophageal cancer. This work may aid the assessment of cancer risk in patients with Barrett's esophagus.

Three of the eighteen Biomarker Developmental Laboratories funded within the Early Detection Research Network, described above, will study markers for development of esophageal cancer. One looks at unique molecular alterations that occur during cellular progression to cancer, and will develop assays to detect cancer-related proteins for diagnosis, screening, prevention, and treatment. Another will measure telomerase activity in body fluids such as plasma to evaluate this as a method for diagnosis as well as an aid during therapy to predict relapse. A third laboratory will identify tumor antigens that induce an immune response, tumor-secreted proteins, and develop assays to test the utility of markers which are found.

In addition, several studies of predictive markers (markers predicting treatment response) have been funded, which can hopefully be used to discern which patients may respond to a particular therapy. Optical techniques for tissue diagnosis without removal of tissue are also under study in the esophagus.

Chemoprevention

There are 3 phase II chemoprevention trials for esophageal cancer, which study the prevention of DNA oxidation by tocopherol and carotenoids, the effect of DFMO in causing dysplasia regression in Barrett's esophagus, and the effect of Celecoxib in causing dysplasia regression in Barrett's esophagus. All of these studies also look at intermediate biomarkers of effectiveness.

Treatment

Esophageal cancer is a treatable disease but it is only rarely curable. The overall 5-year survival rate in those cases amenable to surgery ranges from 5% to 20%. The occasional patient with very early disease has a better chance of survival. Primary treatment modalities include surgery alone or chemotherapy with radiation therapy. Combined modality therapy (chemotherapy plus surgery, or chemotherapy and radiation therapy plus surgery) is under clinical evaluation. Effective palliation may be obtained in individual cases with various combinations of surgery, chemotherapy, radiation therapy, stents, photodynamic therapy,and endoscopic therapy with a laser. Many new approaches to the treatment of patients with esophageal cancer are being tested. The NCI's PDQ data base lists 169 clinical trials open to patients with esophageal cancer. Of these, 112 are trials are NCI-sponsored including 86 Phase I trials wherein new agents are being tested for safety and 4 Phase III trials representing new therapeutic approaches that are closest to introduction into general medical practice.

An increased interest in clinical trials in advanced esophageal cancer has occurred with the demonstration of the activity of several antineoplastic agents. Current studies are evaluating the activity of taxanes, gemcitabine, radiation sensitizing agents, flavopiridol, rebeccamycin analog, irinotecan, oxaliplatin, as well as combination chemotherapy with radiation and surgery.

Stomach cancer is also being extensively studied in clinical trials with 166 open trials for patients with stomach cancer listed in the PDQ database. In this case 110 are NCI sponsored with 87 of these being Phase I trails and 2 being Phase III trials.

Liver/Biliary Tract/Gallbladder/Bile Ducts

Based on SEER data, it is estimated that cancers of the liver and intrahepatic bile duct cancer were diagnosed 14,500 times in the U.S. in 1999 and that 13,600 Americans died of these malignancies. Although hepatocellular carcinoma is a tumor that is relatively uncommon in the United States, its incidence is rising. It is the most common cancer in some other parts of the world. Primary cancers of the liver and intrahepatic bile ducts are far more common in regions of Africa and Asia than in the United States, where they only account for about 1.5% of all cancer cases. It is estimated that hepatocellular carcinoma (HCC) kills more than 1 million people worldwide each year.

NCI's SEER data allow comparison of incidence and mortality among racial and ethnic groups. Non-Hispanic white men and women have the lowest age-adjusted incidence rates (in SEER areas covering 14% of the U.S. population) and mortality rates (for the entire U.S. population) for primary liver cancer. Rates in the black populations and Hispanic populations are roughly twice as high as the rates in whites. The highest incidence rate is in Vietnamese men (41.8 per 100,000), probably reflecting risks associated with the high prevalence of viral hepatitis infections in their homeland. Other Asian-American groups also have liver cancer incidence and mortality rates several times higher than the white population. Age-adjusted mortality rates among Chinese populations are the highest of all groups for which there are sufficient numbers to calculate rates. There were too few cases among Alaska Native and American Indian

populations to calculate incidence or mortality rates. Most cases of liver cancer occur in the two older age groups, but younger adults are often affected in the high risk racial/ethnic groups.

Reported statistics for liver cancers often include mortality rates that equal or exceed the incidence rates. This discrepancy (more deaths than cases) occurs when the cause of death is misclassified as "liver cancer" for some patients whose cancer originated as a primary cancer in another organ and spread (metastasized) to become a "secondary" cancer in the liver. Secondary tumors in the liver is a significant sequelae of a number of other cancers including breast cancer. Understanding the process of matastasis of other cancers to the liver remains a high priority for the NCI.

About two-thirds of liver cancers are classified as HCC, which is the cancer type most clearly associated with hepatitis B and hepatitis C viral infections and cirrhosis. Certain molds that grow on stored foods are recognized risk factors in parts of Africa and Asia. HCC occurs more frequently in men than in women by a ratio of two-to-one. About one-in-five liver cancers are cholangiocarcinomas, arising from branches of the bile ducts that are located within the liver. Certain liver parasites are recognized risk factors for this type of liver cancer, especially in parts of southeast Asia. Angiosarcomas are rare cancers that can arise from blood vessels, including the blood vessels within the liver. They account for about 1% of primary liver cancers and some of them have been associated with industrial exposures to vinyl chloride.

Liver cancer can occur in children. Hepatoblastoma is more common in young children before age 3 and may be caused by an abnormal gene. Children of families whose members carry a gene related to a certain kind of colon cancer may be more likely to develop hepatoblastoma. Children infected with hepatitis B or C virus are more likely than other children to get hepatocellular cancer. Immunization to prevent hepatitis B may decrease the chance of developing hepatocellular cancer, and immunization is recommended for all children.

Liver cancer remains one of the least treatable forms of cancer with overall five-year survival rates of only about 5%. Most cancers are much more treatable when detected early, however even when diagnosed at an early, localized stage, prognosis for liver cancer patients is poor with only a 15 % five-year survival rate. Even so, a significant number of years of life lost could be gained with more effective earlier detection of liver cancer. NCI is seeking to define the genes involved in liver cancer, which may be useful in early detection, and is active in a number of initiatives related to diagnostic imaging.

Three years ago, NCI identified cancer genetics as an area of extraordinary opportunity. We recognized that to exploit fully this area's potential – to move it forward at the accelerated pace that accumulated knowledge and powerful technological advances now permit – new initiatives were needed. Many of today's new opportunities in the area of genetics are a direct benefit of these scientific investments. For example, NCI's Cancer Genome Anatomy Project (CGAP) has resulted in the discovery of approximately 30,000 new genes. New technologies have permitted scientists to determine which genes are expressed (active) in normal and cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as environmental

agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public data bases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome.

NCI has a concerted effort underway to understand the genetic basis of liver cancer. Currently, there are 15 cDNA libraries in CGAP from liver including one library from a liver cancer and one library from tissue classified as liver pre-cancer. Although one of CGAP's aims is to discover genes important to our understanding of cancer development, an important outcome has been the rapid rate of contribution by CGAP to gene discovery overall, which can be reviewed at Summary of CGAP Gene Discovery. CGAP is currently the prime depositor of sequences into the public Expressed Sequence Tag (EST) database. Sequencing from lymphoma and normal lymph node libraries has generated over 58,000 sequences representing nearly 1900 unique genes. Sequences from over 100 unknown unique genes from liver have been entered into the CGAP data base. These unknown unique genes include 83 from normal liver, 21 from liver pre-cancer, and 1 from liver cancer. The CGAP data base serves as a unique resource for researchers seeking to understand liver carcinogenesis. Genes from liver pre-cancer may be particularly useful in accomplishing earlier detection of liver malignancies.

Among patients with underlying cirrhotic disease, a progressive increase in alpha-fetoprotein (AFP) and/or in alkaline phosphatase or a rapid deterioration of hepatic function may be the only clue to the presence of the neoplasm. Tumor markers are substances that can often be detected in higher-than-normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. Tumor markers are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign (noncancerous) conditions. NCI-supported research has established that the biologic marker AFP is useful for the diagnosis of liver cancer. AFP is normally produced by a developing fetus. AFP levels begin to decrease soon after birth and are usually undetectable in the blood of healthy adults (except during pregnancy). An elevated level of AFP strongly suggests the presence of either primary liver cancer or germ cell cancer (cancer that begins in the cells that give rise to eggs or sperm) of the ovary or testicle. Only rarely do patients with other types of cancer (such as stomach cancer) have elevated levels of AFP. Noncancerous conditions that can cause elevated AFP levels include benign liver conditions, such as cirrhosis or hepatitis; ataxia telangiectasia; Wiscott-Aldrich syndrome; and pregnancy. By a radioimmunoassay technique, 50% to 70% of patients in the United States who have HCC have elevated levels of AFP. However, patients with other malignancies (germ cell carcinoma and, rarely, pancreatic and gastric carcinoma) also demonstrate elevated serum levels of this protein. AFP levels have also been shown to be prognostically important, with the median survival of AFP-negative patients significantly longer than that of AFP-positive patients. Other prognostic variables include performance status and liver functions.

Patients scheduled for possible resection require preoperative assessment with angiography in conjunction with helical computed tomographic (CT) scan or magnetic resonance imaging (MRI) with magnetic resonance angiography; these scans have obviated the need for angiography in most patients. Information on the arterial anatomy is helpful for the operating surgeon and may eliminate some patients from consideration for resection. Dynamic CT and MRI scans can document the relationship of the tumor to the hepatic and portal veins (and, on occasion, involvement of these structures), delineating tumors for which the chances for surgical cure are

remote. Laparoscopic evaluation may detect metastatic disease, bilobar disease, or inadequate liver remnant, and therefore obviate the need for open surgical exploration.

HCC is potentially curable by surgical resection, but surgery is the treatment of choice for only the small fraction of patients with localized disease. Prognosis depends on the degree of local tumor replacement and the extent of liver function impairment. Therapy other than surgical resection is best administered as part of a clinical trial. Such trials evaluate the efficacy of systemic or infusional chemotherapy, hepatic artery ligation or embolization, percutaneous ethanol injection, radiofrequency ablation, cryotherapy, and radiolabeled antibodies, often in conjunction with surgical resection and/or radiation therapy. In some studies of these approaches, long remissions have been reported. HCC should be distinguished from bile duct cancer (cholangiocarcinoma) as well as from metastatic cancer that originates in another organ. HCC is associated with cirrhosis in 50% to 80% of patients; 5% of cirrhotic patients eventually develop hepatocellular cancer, which is often multifocal.

The disease known as hepatitis B is caused by the infectious Hepatitis B virus (HBV). HBV alone is estimated to have infected 400 million people throughout the globe, making HBV one of most common human pathogens. In the last few decades, the correlation between HBV and the development of hepatocellular carcinomas (HCC) has been well established. However, the mechanism by which HBV transforms hepatocytes remains elusive.

Vaccines are available against HBV, but they may not be 100% effective against all variants of HBV. Furthermore, there is no cure for individuals already infected. Much more research is needed before we fully understand and can control the spread of this infectious agent. The incidence of hepatitis B increased through 1985 and then declined 55% through 1993 because of wider use of vaccine among adults, modification of high-risk practices, and possibly a decrease in the number of susceptible persons. Since 1993, increases observed among the three major risk groups: sexually active heterosexuals, homosexual men, and injection drug users.
Most people fight off HBV infection themselves. However, approximately 5-10% of those people who are infected with the virus will become carriers, an estimated 5-10% of those people infected each year will progress to chronic liver disease, cirrhosis and possibly liver cancer. There are over a million carriers of the hepatitis B virus in the United States and an estimated 200,000 people contract this serious liver disease each year. An HBV carrier is someone who has had hepatitis B in their blood for more than six months. Children who are infected under age five have a 25%-50% chance of becoming lifelong carriers. A carrier usually has no signs or symptoms of HBV but remains infected with the virus for years or for a lifetime and is capable of passing the disease on to others. Sometimes HBV carriers will spontaneously clear the infection from their bodies, but most will not. Although most carriers have no serious problems with hepatitis B and lead normal healthy lives, some carriers do become sick because they are at significantly higher risk than the general population for liver failure or liver cancer.

The National Cancer Institute supports investigator-initiated research activities on several aspects of the association of HBV and HCC. NCI spent over $10 million on research related to HBV in fiscal year 1998 and expects to spend more than $11 million in fiscal year 2000. Many of the research projects supported by the NCI have as their objective an understanding of the pathogenesis of liver cell injury and HCC in HBV infection. The unifying factor in all of these

studies is our interest in the viral and host determinants, and the virus-host interactions, that are involved in the pathogenesis of this disease.

Before HBV can transform a cell, the virus must first infect it. However, the mechanism through which HBV enters hepatocytes has not been resolved despite further understanding of the viral proteins involved. Another study has shown that the human DNA topoisomerase I enzyme may be important in the circularization, linearization, and possibly integration of viral replication intermediates into host DNA. The integration phenomenon is important in the long term infection with HBV associated with increased incidence of liver cancer.

One of the major impediments to research on viral hepatitis is the lack of good animal models. Because HBV is not infectious in tissue culture and it does not infect immunologically well characterized laboratory animals, the pathogenic mechanisms responsible for liver cell injury and hepatocellular carcinoma in this infection are unknown. One NCI grantee has developed a transgenic mouse model of HBV expression created specifically to provide the opportunity and the reagents needed to pursue these questions directly and definitively. This model has already produced important new insights into the immunobiology and pathogenesis of liver cell injury and hepatocellular carcinoma especially with respect to the role of the viral envelope polypeptides. Recent results from this project strongly suggest that an immune response to the HBV is necessary, and in some cases may be sufficient, to cause liver cancer during chronic HBV infection. The demonstration that cytotoxic T lymphocytes (CTL) initiates the carcinogenic process suggests that therapeutic suppression of antigen nonspecific liver destruction may have a long-term benefit in preventing HCC. The researchers are seeking to establish conditions necessary to induce severe, chronic immunologically mediated liver cell injury in order to determine whether such a disease will lead to the development of hepatocellular carcinoma. The ability of tumor specific CTL to prevent and reverse the development of hepatocellular carcinoma in this model will be assessed. We anticipate that these studies will lead to a better understanding of the pathogenesis of liver cell injury and hepatocellular carcinoma.

Another NCI grantee also working with a transgenic mouse model is exploring the possibility that cellular necrosis and regeneration contribute significantly to carcinogenesis. In chronic HBV infection, there is frequent appearance of so-called ground glass cells, which are hepatocytes with intracellularly retained HBV surface proteins aggregated in the endoplasmic reticulum. Ground glass cells in transgenic mice can cause sufficient hepatocellular damage and regeneration to induce hepatocellular carcinoma. Ground glass cells are known to result from over-expression of the HBV large surface protein, but the molecular events that lead to such over-expression during chronic infection are unknown. Our hypothesis is that HBV genomic mutations that arise during chronic infection comprise one major cause of ground glass cells. During the first 3 years of this project, researchers have been studying in detail the cis-elements of HBV that regulate surface gene expression. As a result, regions of the HBV genome, which when mutated, can cause relative over-expression of large surface proteins and hence intracellular retention of surface proteins in cultured cells have been identified. Interestingly, these regions are frequently mutated during chronic HBV infection. It is anticipated that these studies will lead to new insights on the pathogenesis of ground glass cells, and ultimately of hepatocellular carcinoma in HBV infection.

Another NCI grantee has developed two transgenic mouse models of HCC. In a so-called "immune" model, HCC occurs after several months of chronic hepatitis due to a persistent HBV-specific cytotoxic T lymphocyte response in mice that produce nontoxic amounts of HBV envelope proteins. In the "storage" model, HCC occurs after several months of chronic hepatitis caused by the overproduction of nonsecretable subviral filaments that accumulate in the endoplasmic reticulum and lyse the hepatocyte, triggering a necroinflammatory liver disease that stimulates hepatocellular proliferation, macrophage activation and inflammation, oxidative DNA damage, aneuploidy, preneoplastic foci and the development of HCC.

Recently these investigators discovered that, in addition to causing hepatitis, progressive filament retention inhibits hepatocellular apoptosis in theses animals. These provocative observations suggest that L-HBs retention may contribute to the development of HCC not only by causing the necroinflammatory regenerative liver disease that creates the genotoxic milieu in which transforming mutations can occur, but also by inhibiting apoptosis and preventing the elimination of transformed hepatocytes. The major thrust of the current investigation is to determine whether L-HBs regulates apoptosis directly or indirectly in the "storage" model of HCC and, if so, how.

Other investigations in animal models have demonstrated a cellular and humoral immune response to HBV structural proteins following DNA-based immunization. Studies are continuing to identify the most immunogenic antigens for future immunotherapeutic approaches to chronic HBV infection.

Yet another NCI grantee aims to investigate a transgenic model for the role of HBV in HCC, derived from the demonstration that the HBV transactivator X protein (HBx) interacts with a cellular protein involved in nucleotide excision repair, and that HBx expression inhibits normal DNA repair. It is known that all cancers involve the accumulation of genetic alterations. The rate of this accumulation would be predicted to be dependent upon the efficiency of DNA repair. In this NCI-supported study, the effect of HBx on mutation frequency will be tested utilizing HBx transgenic mice.

The impact of HBx on DNA repair may be related to its involvement in apoptosis, cellular suicide that normally occurs as a result of unrepaired DNA damage. An NCI grantee is now testing the hypothesis that HBxAg alters the sensitivity of primary rat hepatocytes to drug induced apoptosis. This will be done by asking whether HBxAg can replace or complement other oncogene products, such as adenovirus E1A or E1B, mutant p53, and activated ras in overcoming apoptosis, and in some cases, stimulating cell growth. Given that HBxAg binds to p53, and the centrality of p53 to apoptosis, another aim of this project is to test the hypothesis that HBxAg acts by altering p53 dependent biochemical pathways important to hepatocellular growth and apoptosis. It is hoped that this work will also provide opportunities for the establishment of cellular and biochemical assays capable of screening drugs which effect pathways important to the pathogenesis of chronic HBV infection and the development of hepatocellular carcinoma.

Thus the NCI is supporting an active research program which stresses the development of animal models for human hepatocellular carcinoma, and the use of such model systems and in vitro approaches to identify mechanisms by which the hepatitis B virus causes human liver cancer, as well as the development of possible therapeutic or preventive modalities that can reduce the burden or morbidity and mortality associated with long-term infection with HBV.

Hepatitis C

The hepatitis C virus (HCV) is another of the six viruses (A, B, C, D, E and G) that together account for the majority of cases of viral hepatitis. According to the National Health and Nutrition Examination Survey of 1988-94 and other population-based surveys, nearly four million Americans are infected with hepatitis C. The infection is more common in minority populations (3.2 percent of African-Americans and 2.1 percent of Mexican-Americans) than in non-Hispanic whites (1.5 percent). Approximately 30,000 acute new infections are estimated to occur each year, about 25-30 percent of which are clinically diagnosed, and HCV accounts for 20 percent of all cases of acute hepatitis. HCV is responsible for an estimated 8,000-10,000 deaths annually, and without effective intervention that number is postulated to triple in the next 10-20 years. The virus is now the leading reason for liver transplantation in the United States, and is recognized as a significant etiological agent for hepatocellular carcinoma.

The NIH consensus conference on Management of Hepatitis C held March 24-26, 1997 made a number of recommendations concerning research opportunities. Among these was that the mechanism of development of hepatocellular carcinoma in patients with hepatitis C infection needs elucidation. The consensus conference also noted the need for vaccines and new antiviral agents, and indicated that vaccine development will require a better understanding of both cellular and humoral immunity to HCV, the nature of antigenic variation of the virus, and the mechanism(s) by which HCV regularly escapes the host immune system and establishes persistent infection. The absence of suitable animal and tissue culture models of HCV infection and disease progression, including cancer, was also noted by the conference to be "a major bottleneck" and their development to be a "high priority." In recognition of the significant role of hepatitis C in the etiology of human liver diseases, including cancer, new multi-Institute Requests for Grant Applications have been issued to address many of these issues. These initiatives, and other research activities, result in part from the activities of the NIH HCV Working Group, a group consisting of representatives from several NIH Institutes and Centers, including NCI, with an interest in HCV infection and its sequelae including cirrhosis and liver cancer.

In fiscal year 1998, the NCI spent $2.153 million on research related to hepatitis C, and NCI spending on hepatitis C is expected to reach $2.4 million in fiscal year 2000. The NCI coauthored and co-funded a Request for Applications (RFA) for "Hepatitis C: Natural History, Pathogenesis, Therapy and Prevention" which supported high quality research to address many of the recommendations of the 1997 NIH Consensus Conference. Of the total of $5.15 million set aside by NIH Institutes and Centers for the first year of funding of this RFA, the NCI contributed $1.2 million in fiscal year 1999, to fund high quality applications dealing with protective immunity, immunotherapy, and vaccines for HCV, and with epidemiologic and

natural history studies of human HCV infections. These grants will be funded for the full five year terms recommended by the review group.

An additional RFA, utilizing the Small Business Innovative Research mechanism was reviewed in fiscal year 1999 and will be funded in fiscal year 2000. NIAID and NCI are each contributing up to $1.5 million to this RFA, and the NCRR, NIDDK, and NIAAA have also committed funds. This targeted effort will encourage small businesses to participate in the development of small animal models for studies of pathogenic and cancer causing properties of HCV, as recommended by the Consensus Conference.

In addition to the newly funded grants mentioned above, the NCI is currently supporting traditional research grants on Hepatitis C virus. Three virology grants include studies on virus replication, host and viral factors responsible for HCV persistence and disease production, and development of possible antivirals and vaccines for HCV. An infectious disease epidemiology grant includes HCV as a part of a larger study of the epidemiology of human T-lymphotrophic virus in Japan. Although these grants were funded prior to the 1997 NIH Consensus Conference on HCV, all of them are directly related to the research goals of understanding how HCV causes human cancer and developing vaccines to prevent the initial infection with HCV suggested by participants in the Consensus Conference.

NCI intramural scientists are utilizing molecular genetic and clinical epidemiological approaches to characterize variations in more than 25 genes that affect infection or disease progression following exposure to HCV and other viral pathogens. In addition, the rates of infection with HCV and the human immunodeficiency virus have been followed since 1982 in a cohort of more than 2000 persons with hemophilia in the Multi-center Hemophilia Cohort Study. This study demonstrated that, after AIDS, hepatic failure was a leading cause of death among persons with hemophilia.

NCI staff are active participants in the NIH HCV working group, whose function is to plan and develop an NIH-wide strategy for dealing with HCV infection and all of its sequelae, from cirrhosis through cancer. The working group has prepared a draft strategic plan for studies on etiologic mechanisms, prevention (including preventive vaccines), new diagnostic and prognostic tests, and novel therapeutic measures. It is anticipated that this draft strategic plan will be reviewed by extramural scientific experts and the NIH Institutes and Centers with an interest in HCV and/or liver cancer before being submitted to the NIH for formal approval. As a result of the two previously mentioned cooperative RFAs, NCI has substantially increased its research investment in studies of the virology and epidemiology of HCV as it relates to causative mechanism(s) of human liver cancer. The Institute will continue to support research as well as workshops or conferences to determine the scientific state of the art in HCV research. These workshops will also solicit the best professional judgement recommendations for research activities on the role of HCV in human cancer, and in the longer term, possible preventive or therapeutic approaches for decreasing or eliminating this disease from our population.

As in the case of HBV, progress in our understanding of HCV and the development of effective treatment modalities have been hampered by lack of a reliable in vitro system for propagating HCV and of a convenient animal model. Recently, an NCI grantee has developed two long-term

cell culture systems of HCV by transfection with infectious HCV RNA transcripts producing high levels of HCV and HCV transgenic. These model systems may prove invaluable for assessing the impact of potential treatments for HCV.

Another NCI grantee has constructed a full length cDNA clone of the HCV genome and performed intrahepatic inoculation of RNA transcripts of that clone in chimpanzees resulting in HCV infection and hepatitis clinically indistinguishable from infections caused by inoculation of HCV containing serum. These investigators are now performing a prospective study on humoral and cellular immune responses to HCV infections and viral sequence evolution in infected chimpanzees aiming to define how the virus-host interactions differ between animals that resolve their infections and those that become persistently infected. Recovered animals will be challenged with homologous and heterologous virus to test whether they are protected from reinfection. It is believed that much of the information gained in these studies will be applicable to HCV vaccine development for man.

Hepatitis B infection and hepatitis C infection appear to be the most significant causes of HCC worldwide, particularly in patients with continuing antigenemia and in those who have chronic active hepatitis. A series found that male patients older than 50 years of age who have both hepatitis B and hepatitis C infection may be at particularly high risk for liver cancers. Aflatoxin has also been implicated as a factor in the etiology of primary liver cancer in parts of the world where this mycotoxin occurs in high levels in ingested food. Workers who were exposed to vinyl chloride before controls on vinyl chloride dust were instituted developed sarcomas in the liver, most commonly angiosarcomas. Other sarcomas of smooth muscular and vascular origin are also found.

In total NCI's spending on liver cancer for fiscal year 1998 was over $38 million and should approach $42 million in fiscal year 2000. The NCI currently funds 83 research projects related to hepatocellular carcinoma. Several investigator-initiated grants are studying the genetics of carcinogenesis in the liver. Topics include tissue specific regulation of the c-myc protooncogene, the RIZ gene (binds the retinoblastoma protein) in tumorigenesis, developmental and neoplastic gene expression in the liver, and isolation of a liver tumor suppressor gene on chromosome 11.

The NCI's PDQ data base lists 173 open trials for patients (either adults or children) with liver cancer. Of these 110 are NCI-sponsored including 86 Phase I trials intended to assess the safety of novel new treatment regimens and 2 Phase III trials in which new treatment approaches are closest to general medical practice.

Item

Head and Neck Carcinoma -- Head and neck squamous cell carcinoma continues to be the most common from of head and neck cancer. The Committee encourages NCI to enhance research on the mechanisms of tumor-induced immunosuppression through all available mechanisms, as appropriate, including specialized projects of oncology research excellence. (p.68)

Action taken or to be taken

Gene Therapy and Oncolytic Viruses -- Cancer accounts by far for most of the gene therapy trials that are being carried out both in the United States and worldwide. One hundred seventy-three of the 248 gene therapy protocols that have been reviewed by the National Institutes of Health Recombinant DNA Advisory Committee are for the treatment of cancer. Of these cancer gene therapy protocols, two-thirds are for cancer immunotherapy, involving transfer of cytokines, immune accessory molecules, or tumor antigens into a variety of cellular targets. The majority of the remaining protocols involve the transfer of chemoprotection (e.g., the multi-drug resistance gene), prodrug activation (e.g., herpes thymidine kinase, which activates ganciclovir), or tumor suppressor genes (e.g., p53).

Two agents are highlighted below. One, Ad5CMV-p53, is a replication-defective adenovirus that has been engineered to deliver the p53 tumor suppressor gene to tumor cells. The other, ONYX-015, is a conditionally replication-competent adenovirus that is capable of destroying tumor cells during the replicative cycle of the virus. Both of these agents have shown sufficient promise in phase I and phase II clinical trials so that phase III clinical trials are planned to test their efficacy in the treatment of head and neck cancer.

Ad5CMV-p53

Ad5CMV-p53 (NSC# 683550; Introgen Therapeutics, Inc.) is a replication-defective adenoviral vector which contains a CMV promoter and the wild type p53 gene. The p53 gene is a tumor suppressor gene, which in the presence of damaged cellular DNA encodes a phosphoprotein that induces a G1 arrest prior to replication of the genome. This process allows the cell either to repair itself or to progress to apoptosis (programmed cell death). A mutation in the p53 gene occurs in approximately half of all tumors and is the most common genetic abnormality found in human cancers. A mutated p53 gene produces a defective protein that lacks the ability to stop division of damaged cells, thereby permitting continued cellular proliferation. Moreover, p53 is required in order for many chemotherapy agents to activate apoptosis in tumor cells. In preclinical studies, injection of Ad5CMV-p53 into tumors induced apoptosis in variety of tumor cells which lacked functional p53 and inhibited the growth of tumors in animals. Ad5CMV-p53 also demonstrated synergistic activity when combined with cisplatin or radiotherapy in preclinical animal models. Interestingly, p53 gene transfer has exhibited bystander effects, mediated through either the repression of vascular endothelial growth factor expression – thereby inhibiting tumor angiogenesis – or by increasing the expression of Fas and Fas ligand.

In a phase I trial of Ad5CMV-p53 in advanced recurrent head and neck squamous cell carcinoma, up to 10^{11} plaque-forming units (pfu) were injected into the tumors of 33 patients, either alone (TIW x 2 weeks, repeated monthly) or with surgery (a dose given before, during, and after surgery). Other than moderate pain on injection, transient fever, and headache, the treatment was well tolerated and dose-limiting toxicity was not observed. There were partial responses (PR) in 2 of 17 patients given Ad5CMV-p53 alone, and one complete response (CR) out of 16 patients who also underwent surgical resection. Three phase II trials of intratumorally-administered Ad5CMV-p53 were carried out in 145 evaluable patients with recurrent squamous cell carcinoma of the head and neck. Up to 2.5×10^{12} vector particles were administered in

multiple schedules for a duration of up to 11 months. The objective response rate was 4%; stable disease was observed in an additional 22% of patients. Adverse events included self-limited fever and chills (52%), injection site pain (39%), nausea (11%), and injection site bleeding (12%). A maximal tolerated dose was not reached.

In a phase I/II trial of Ad5CMV-p53 in advanced non-small cell lung carcinoma, up to 10^{11} pfu of Ad5CMV-p53 were injected into tumors, either by bronchoscopy or with CT guidance. The agent was given alone or with cisplatin 80mg/m^2 2 days prior to Ad5CMV-p53 administration. Patients experienced transient grade 3 fever or nausea, although a maximum tolerated dose was not reached. Two of 26 and three of 23 patients achieved a PR in the Ad5CMV-p53 group and Ad5CMV-p53 + cisplatin group, respectively. Progression-free survival was longer in the Ad5CMV-p53 + cisplatin group, as compared to the Ad5CMV-p53 group.

NCI-CTEP, in collaboration with Introgen Therapeutics and RPR Gencell, is sponsoring a number of single agent phase I trials in solid tumors, including ovarian, breast, bronchioloalveolar, and hepatocellular carcinomas, as well as in malignant glioma. In addition, Ad5CMV-p53 is being combined with radiation therapy in the treatment of recurrent non-small cell lung carcinoma. Correlative studies will include viral shedding as well as gene transfer and apoptosis in tumors when possible.

ONYX-015

ONYX-015 (Onyx Pharmaceuticals, NSC #688653) is an oncolytic adenovirus with a deletion in the 55 kiloDalton E1B gene that reportedly allows the virus to replicate selectively in and destroy cells lacking p53 function. However, other reports recently have questioned the relationship of ONYX-015 replication to p53 function. ONYX-015 cytolytic has also been shown in preclinical studies to be enhanced by concomitant administration of chemotherapy. In a recently completed phase II trial, 30 patients with head and neck cancer who had relapsed following surgery and radiation were treated with intratumoral injections of ONYX-015 in combination with cisplatin/5-fluorouracil chemotherapy. There were 6 CR and 10 PR, for an overall response rate of 62%. Responses were observed in patients both with and without p53 gene mutations. The treatment was well tolerated, with toxicities that were expected with chemotherapy alone. A randomized 2-arm study will compare ONYX-015 plus 5-FU/cisplatin to chemotherapy alone. Primary endpoints will be progression-free survival and durable tumor responses. ONYX-015 is also being evaluated in company-sponsored trials in ovarian and colorectal cancer metastatic to the liver. In addition, Onys-015 is being administered as a chemoprevention agent for the treatment of oral dysplasia. NCI/CTEP is sponsoring a phase I clinical trial of ONYX-015 in malignant gliomas and a phase II trial in hepatobiliary malignancies.

Other oncolytic viruses that have entered or are soon to enter the clinic include herpes virus, Newcastle disease virus, and reovirus. All these viruses have been shown to replicate selectively in cancer cells, albeit by different mechanisms. Reovirus, for example, requires the presence of an activated Ras signaling pathway in order to replicate and destroy cells. In addition, one can confer selectivity by placing an essential viral gene under the control of a tumor-specific promoter. This approach is being explored in prostate cancer, where the adenoviral E1A gene is

regulated by the prostate-specific antigen (PSA) promoter. Since all these viruses can replicate conditionally – and spread - in tumors, they may serve as more effective gene vectors for cancer gene therapy. For example, by inserting a cytokine gene into these viruses it may be possible to enhance oncolysis by generating anti-tumor immunity.

Another new approach is the use of novel antigen delivery systems such as Listeria monocytogenes, a gram positive bacterium that is able to enter host cells, escape from the endocytic vesicle, multiply within the cytoplasm and spread directly from cell-to-cell without encountering the extracellular milieu. The ability of the bacterium to gain access to the host cell cytosol allows proteins produced by the bacterium, such as tumor rejection antigens, to efficiently turn on the MHC class I antigen processing and presentation pathway - thus acting as an anti-tumor vaccine. Animal studies are ongoing testing this system for the expression of melanoma-specific antigens.

Clearly, much work needs to be done, both in the laboratory and in the clinic, in order to exploit the full potential of these novel viral and bacterial therapies.

Tumor-Induced Immunosuppression in Head and Neck Cancer

Tumor-induced immunosuppression refers to the phenomenon that the immune system of some cancer patients is incapable of attacking the tumor as a result of exposure to as yet unidentified products produced by the tumor cells. If true, this will limit the ability of immunotherapy approaches, including vaccine approaches, to cure these tumors. This phenomenon is not observed in every patient or in every tumor type. Given the enormous differences in behavior among cancer cells, this variability is to be expected, but it has made research quite difficult. Head and neck cancer is prominent among the tumor types in which immunosuppression has been studied, particularly at the Pittsburgh Cancer Institute. Overall, the phenomenon is under study by approximately a dozen laboratories, many of which are supported by the National Cancer Institute. Because of the importance of the subject, the difficulties inherent in the research, and the wide spectrum of results reported, the NCI has made significant efforts to facilitate this field of research by convening workshops in which all of the active investigators can present their results and discuss unified approaches to the most important research questions. In September 1998, the NCI sponsored a workshop entitled Mechanisms of Immune Evasion by Tumors. Included in this workshop were two scientists primarily working on head and neck cancer. The results of this workshop were published in a prominent scientific journal, which has resulted in an increase of grant applications in this area. A second workshop was sponsored in August 1999, entitled Tumor Escape from Immune Recognition: Molecular and Functional Significance. Some of the same scientists attended this second workshop, along with some new investigators. A summary of this workshop will also be published. Grants funded in the last two years show significant promise to elucidate the mechanisms underlying tumor-induced immunosuppression. Once the mechanisms are known, it will be possible to apply recent discoveries in immunology to devise methods to prevent or reverse immunosuppression, making immunotherapy an attractive method to eradicate these tumors.

Support for Translational Research of Head and Neck Cancers

The NCI recognized the need to support multidisciplinary translational research on head and neck cancers and co-funded since 1996 three Oral Cancer Research Centers (OCRC) with the National Institute of Dental and Craneofacial Research (NIDCR). These OCRC included U Alabama, UC San Francisco, and U Chicago with total costs of $5.5 million to the NCI over a period of five years. These awards are not expected to be renewed by NIDCR when they expire in the fall of 2001. The NCI recognizes that a substantial gap may be created if the support for translational research in this area would not be continued. It is the intent of the NCI to continue to support multidisciplinary translational research on head and neck cancers by implementing a SPORE program in this important area. SPOREs support a mix of basic and clinical researchers whose interactive and collaborative research efforts will result in new approaches for early detection, diagnosis, therapy, and prevention and control. Applications for head and neck SPOREs will be accepted on the October 1, 2001 receipt date and awards are expected to be made in early 2002.

Item

Lymphoma -- Despite strides made in other forms of cancer, the rate of incidence of lymphoma is increasing. Lymphoma is the second fastest growing cancer by rate of incidence. The Committee encourages NCI to enhance lymphoma research, promote new innovative research models based on collaborative methods to maximize current lymphoma research conducted at NCI, collaborate research efforts with NIEHS to explore environmental factors as causes of lymphoma, and collaborate research efforts with CDC. The Committee also encourages NCI to consider exploring research in currently incurable lymphomas such as low-grade and aggressive incurable lymphomas. (p.68)

Action taken or to be taken

NCI's Surveillance of Lymphoma

The magnitude and trends in lymphoma are being tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. An estimated 64,000 cases of lymphoma were diagnosed in America in 1999 and an estimated 27,000 Americans died of the disease. These SEER statistics mean that lymphomas, which include Hodgkin's disease and non-Hodgkin's lymphoma, are the fifth most common type of cancer diagnosed and the sixth most common death in the United States. Whereas most cancer rates have been declining in the 1990's, lymphoma rates have risen for reasons that are not clear. Of the two basic lymphoma types, non-Hodgkin's lymphoma is far more common with 56,800 cases as compared to 7,200 for Hodgkin's disease. The 1-year survival rates for Hodgkin's and non-Hodgkin's lymphoma are 93% and 70%, respectively with 5-year survival rates being 82% and 51%, respectively.

Interestingly, the age-adjusted incidence rates for non-Hodgkin's lymphoma are higher among men than women in every racial/ethnic group except Koreans, in which there is a slight preponderance among women. In both men and women, non-Hodgkin's lymphoma incidence rates are highest among non-Hispanic whites (19.1 and 12.0 per 100,000 men and women,

respectively) and lowest among Koreans (5.8 and 6.0 per 100,000). This corresponds to a high to low ratio of the rates (white non-Hispanic to Korean) of 3.3 for men, and 2.0 for women. Vietnamese men have the second highest rates (after whites), followed by white Hispanic, black, Filipino, Hawaiian, Chinese and Japanese men. There were too few cases diagnosed in Alaska Native and American Indian (New Mexico) men to calculate reliable rates. Among women, white Hispanics accounted for the second highest rates, followed by Filipino, Japanese, black and Chinese women. There are insufficient numbers of lymphoma cases diagnosed in Alaska Native, American Indian (New Mexico), Hawaiian and Vietnamese women to estimate their rates reliably.

Age-adjusted mortality rates of non- Hodgkin's lymphoma are consistent with the incidence rates with one exception: the mortality rate for Hawaiian men
(8.8 per 100,000) exceeds that of any other group, even though the corresponding incidence rate is considerably lower than that of white non-Hispanics. There are an insufficient number of deaths from non-Hodgkin's lymphoma among Hawaiian women to reliably assess the mortality rate for that group.

In every group, incidence rates increase with age, however the magnitude of this increase varies by racial/ethnic group. For example, from ages 30-54 years to ages 70 years and older, the incidence of non- Hodgkin's lymphoma increases about five- fold among white non-Hispanic men, but 11-fold among Filipino men. Among women, the comparable rates increase eight- fold among white non-Hispanics, but 16- fold among Filipinos. These differences reflect high incidence rates among older Filipinos, similar to those of white non- Hispanics. These high rates are not reflected, however, in the mortality data for Filipinos. Among those aged 30-54 years rates among black men and women are close to those among white non-Hispanics. Rates among black men and women aged 70 years and older, however, are only about one-half those of white non-Hispanics.

Hodgkin's disease is considerably less common than non-Hodgkin's lymphoma. As a result, reliable incidence and mortality rates are available only for black, Hispanic and white populations. In both men and women, overall age-adjusted incidence rates are highest among white non-Hispanics, and considerably lower in black and Hispanic populations. Incidence rates are higher in men, compared to women, in each racial/ethnic group.

Among women 30-54 years of age, Hodgkin's disease rates are highest in the white non-Hispanic population, slightly lower in the black population, and considerably lower among Hispanics. Only in the white population are reliable rates available in the other age groups. Rates among white non-Hispanic women aged 70 years and older are about 50% greater than in the two younger groups. The rates among black men and white non-Hispanic men are similar in both the 30-54 and 55-69 year age groups. The rate in white Hispanic men aged 55-69 years (5.1 per 100,000), however, is almost double that of the younger white Hispanics (2.7 per 100,000). Rates for men over age 70 years are available only for the white population and are about one-third higher than those for the younger age groups.

Lymphoma Etiology

Identifying causes and risk factors associated with lymphomas has remained a formidable challenge to investigators, particularly with the growing recognition that there are several types of tumors that behave differently. The NCI has been a leader in conducting lymphoma research in human populations, sponsoring a symposium in 1992 for discussing what research advances are needed. With the observed increasing incidence rates in the U.S. population, lymphoma research that examines the role of environmental factors is of particular interest to the Institute. Altered immune function, whether due to exposure to specific viruses (such as HIV and HTLV-I), or due to other causes, clearly puts people at higher risk. Herbicides and other chemicals may also increase the risk of these diseases. It does appear that reduced immune function is a major risk factor for lymphoma. Persons with organ transplants are at a higher risk due to altered immune function. Both major types of lymphoma, Hodgkin's disease and non-Hodgkin's lymphoma, may occur in AIDS patients. Also, the intermediate-and high-grade types of non-Hodgkin's lymphoma are more commonly found in AIDS patients. Both types of lymphomas can also occur in adults and in children.

The incidence of AIDS-associated cancers has increased dramatically in the last ten years. In patients infected with the human immunodeficiency virus (HIV), about one-half of all B-cell lymphomas are EBV-associated, including virtually all primary central nervous system lymphomas in patients with AIDS. Additionally, the human T-lymphotropic virus 1 (HTLV-1) is associated with lymphomas and leukemias. Current research focuses on understanding the role of viral genes in the initiation and progression of viral-associated lymphomas to provide the basis for future investigations on treatment strategies.

NCI has had a long history of leading the effort to determine the extent to which environmental and occupational agents contribute to the burden of cancer. NCI has a broad and wide-ranging research program of laboratory and epidemiologic investigations into the links between cancer and exposures to pesticides, air pollution, drinking water contaminants, electromagnetic and ionizing radiation, lifestyle and other factors. Environmental studies are especially challenging. Because such exposures are indirect and experienced passively, and often they occurred a long time in the past, it is difficult to quantify the long-term dose to any individual, who may not know whether and to what extent they were exposed to any pollutant. In addition, pollutants are ubiquitous and occur in the ambient environment at very low levels. Exposure is hard to measure accurately, and low levels of exposure may be associated with only small increments in risk, also hard to assess statistically. Biomarker approaches (genetic, molecular, cellular, tissue or organ-specific) are one way to assess internal dose, and are a major thrust of current research work. There has been particular interest in identifying markers of cancer risk; for example, for detecting and quantifying influential environmental exposures, as indicators of mechanisms relating exposures and cancer, or as measurements of individual susceptibility to cancer.

In 1999, NCI in collaboration with NIEHS convened an ad hoc advisory group of interdisciplinary experts to discuss the present status of environmental exposure assessments for research in cancer epidemiology. Considerations for advancing the field that could be addressed during the next five years were summarized, focusing on research needs and new research directions. NCI and NIEHS program staff are currently preparing a request for applications

(RFA) on exposure assessment incorporating the meeting discussion. It is expected that the RFA, entitled Exposure Assessment in Cancer Epidemiology, will be issued and funded in fiscal year 2000.

NCI-Sponsored Lymphoma Research

NCI supports a very large research project portfolio related to lymphoma comprised of over 400 individual projects and expects to spend $73 M on lymphoma research in FY 2000. The aims of NCI's research projects are highly diverse and include understanding the molecular lesions relevant to the pathogenesis of lymphomas; understanding the role of Epstein-Barr virus (EBV) in EBV-related malignant diseases, with an emphasis on malignant lymphomas; development of potentially novel approaches to cancer therapy by targeting viral genes or genetic abnormalities; developing chemotherapeutic regimens designed to achieve cure in patients with lymphomas, while minimizing toxicity; defining risk groups using clinical and biological parameters; and promoting the utilization of the overall expertise in lymphoid malignancies at NCI for the benefit of patients with lymphomas. The NCI has supported and continues to support many basic and clinical research programs that are attempting to better characterize the immunology and biology of lymphomas, and to increase the potential for cure of these patients. Perhaps more than in any other tumor type, lymphoma research has produced an enormous knowledge base about these tumors, so that we have a better understanding of their biology. In particular, studies in NHL have led to the concept of a defect in programmed cell death, or apoptosis, as critical to the development of lymphomas. An increasing number of genes related to this process have been identified.

Dramatic scientific advances have led to new and fundamental insights into the causes of cancer. Fueled by conceptual and technical breakthroughs, the often breathtaking pace of scientific discovery has engendered a tremendous sense of optimism among cancer researchers that new avenues will be found to detect, treat, and prevent cancer. Nowhere is this sense of promise greater or the potential implications more profound than at the interface of the fields of epidemiology and genetics. By marrying the epidemiologic approach – study of the distribution and causes of cancer in human populations – with cutting-edge genetic and related molecular technologies, we will be able to:

- Identify genes that predispose people to cancer (cancer susceptibility genes) whose pathways of action will point to previously unsuspected environmental carcinogens, including those related to lifestyle exposures.
- Detect the slight to moderate elevations of risk resulting from certain types of exposures by studying genetically susceptible subgroups.
- Design new approaches to diagnose, prevent, and treat cancer based on an understanding of how genes modify and interact with environmental exposures.
- Quantify cancer risks associated with gene-environment interactions, which will direct individual and public health strategies aimed at preventing and controlling cancer.

The importance of lifestyle and other environmental exposures as causes of cancer is unquestionable. The pivotal role of environment is reflected in the substantial variation in cancer incidence around the world, and in the changes in risk observed among groups that migrate and

become acculturated in the host country. Furthermore, epidemiologic research has succeeded in identifying a wide range of cancer-causing exposures, including tobacco use, dietary components, sunlight, ionizing radiation, environmental chemicals, infectious agents, obesity, exercise, hormones, and reproductive factors. Nevertheless, the causes of many cancers remain elusive. While better approaches to measuring exposures will provide new insights, it is clear that the environment represents only part of the equation in determining who will get cancer. It also is important to understand cancer susceptibility. For example, why does one person with a cancer-causing exposure (such as smoking or infection with human papillomavirus) develop cancer, while another does not?

Viewing such questions through the lens of genetics promises to provide insights into these apparent paradoxes. The scientific investment in cancer genetics, initially focused on the intensive study of rare cancer-prone families, already has paid huge dividends. These studies have opened a unique window into the basic mechanisms of cancer, with benefits extending well beyond the rare families from which they were derived. This is because the genes identified by these studies are altered forms of normal genes involved in key biochemical chains of events (pathways) controlling fundamental cell processes. It has become clear that these same pathways contribute to the development and progression of the more common, non-hereditary forms of cancer. Yet even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified by other genetic and environmental factors. There is mounting evidence that one's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures. Opportunities now exist to determine how variations in these genes combine with environmental and other factors to induce cancer in the general population.

Three years ago, NCI identified cancer genetics as an area of extraordinary opportunity. We recognized that to exploit fully this area's potential – to move it forward at the accelerated pace that accumulated knowledge and powerful technological advances now permit – new initiatives were needed. Many of today's new opportunities in the area of genetics are a direct benefit of these scientific investments. For example, NCI's Cancer Genome Anatomy Project (CGAP) has resulted in the discovery of approximately 30,000 new genes. New technologies have permitted scientists to determine which genes are expressed (active) in normal and cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as environmental agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public data bases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome.

These advances are ushering in a new generation of epidemiologic research that will lead to a comprehensive understanding of environmental and genetic determinants of cancer. However, the exciting opportunities of this emerging field – referred to as "molecular epidemiology" – are accompanied by enormous challenges. Population studies sufficiently powerful to examine the complex interactions of multiple genetic and environmental factors will involve unprecedented numbers of participants and will require new research infrastructures and strategies for interdisciplinary collaboration.

NCI has a concerted effort underway to understand the genetic basis of lymphoma. Currently, there are 4 cDNA libraries in CGAP from lymphoma and 3 from normal lymph node tissue. Although one of CGAP's aims is to discover genes important to our understanding of cancer development, an important outcome has been the rapid rate of contribution by CGAP to gene discovery overall, which can be reviewed at Summary of CGAP Gene Discovery. CGAP is currently the prime depositor of sequences into the public Expressed Sequence Tag (EST) database. Sequencing from lymphoma and normal lymph node libraries has generated over 58,000 sequences representing nearly 1900 unique genes. Sequences from nearly 500 unknown unique genes from lymphoma have been entered into the CGAP data base.

Newly developed tools are helping scientists perform large-scale analyses of the vast human genome to genetically characterize tumors, information that can help to explain why patients diagnosed with the same cancer differ dramatically in their responses to treatment, and in their prognoses. For example, the Lymphochip, a computer chip-like device with DNA from more than 15,000 genes important to both the immune system and lymphoid cancers, is enabling researchers to study the genes active in non-Hodgkin's lymphoma. The Lymphochip promises to be a useful tool for detecting lymphomas early, analyzing risk, and selecting targeted treatments. A similar device, an affinity-based biochip, was developed by NCI and FDA investigators to generate biomarker profiles of normal, precancerous, cancer, and metastatic cells from esophageal, prostate, colon, and liver tissues. Biomarker pattern profiles reveal changes in protein expression as tissue cells transition from normal, to premalignant, to invasive cancer; this new technology could be extremely useful in the discovery of disease-related proteins, therapeutic assessment, and treatment toxicity monitoring.

At the molecular level the genetic lesions associated with or contributing to the etiology of lymphoma are chromosomal translocations causing aberrant patterns of proto-oncogenes normally expressed, or the expression of proto-oncogenes not normally expressed, in lymphoid cells. These genes are generally in the family of transcription factors, which are proteins required for gene expression. In addition, a unique family of proteins that suppress programmed cell death or apoptosis, typified by bcl-2, has also been identified, and contributes to the development of some lymphomas.

Categories of research currently supported by NCI and examples of lymphoma research in human populations within each category, include:

- Studies of Non-Hodgkin's disease lymphomas in children and adults assessing the roles of the Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) in conjunction with non-infectious environmental factors (e.g., hair-coloring products, pesticides, nitrates, solvents, and other industrial chemicals).
- Molecular studies of immune factors associated with AIDS-related lymphoma.
- Research measuring genetic changes in tumor cells for comparing HIV positive and negative patients with NHL.
- Large population studies of NHL to evaluate the influence of childhood infections, autoimmune diseases and chronic infections, UV light exposure, vaccinations, medicinal drugs, and exposure to EBV and other viruses.
- Research on pesticides and their effect on the occurrence of NHL.

- Studies in women to determine whether hair-dye use increases risk of NHL
- Analytical methods for estimating risk of subtypes of NHL associated with occupational and environmental (e.g., herbicides, solvents, asbestos, radiation) exposures.

The NCI supports a national program concerning the viral etiology and biology of lymphoid malignancies in humans. Specifically, the Institute supports basic research on both human and animal DNA and RNA containing viruses that are known etiologic factors and/or cofactors in the initiation and progression of lymphoid malignancies. One of the great contributors to the rise in NHL recently has been AIDS. Between 1993 and 1999 the NCI published numerous Program Announcements and Requests for Applications in the NIH Guide that were directly aimed at encouraging and supporting research in AIDS-related lymphoma. Many current basic research grants were submitted and funded in response. New initiatives are currently under development.

New NCI research initiatives that are already underway:

- In collaboration with NIOSH/CDC and other NIH institutes, NCI is supporting two Requests for Applications and a Program Announcement on exposure measurement, elucidation of low levels of exposure, farmworker surveillance, and development of biomarkers for environmental and occupational studies, including lymphoma.

- The Cancer Genetics Network is designed to conduct research and clinical trials to evaluate new approaches to cancer screening and preventive interventions such as dietary or environmental changes and chemoprevention, particularly for individuals with genetic predisposition for cancer, including lymphoma. Pilot research projects are underway and will provide a basis for larger studies.

- Research priorities that have been identified also include improving the accuracy of our measurement and estimation of exposure, particularly if historical, to environmental agents and expanding our approaches to study design and analysis for conducting environmental research that focuses on gene-environment interactions. This priority area will be encouraged and supported through a Request for Applications to be issued in collaboration with NIEHS in 2000. This work has direct application to enhancing lymphoma research.

- The NCI is proceeding rapidly with plans to organize and support a meeting next spring on state-of-the art NHL research. The major focus of the workshop will be to gain insights from ground-breaking immune system-related laboratory and clinical research that could open avenues for a "new generation" of epidemiologic studies into the causes and increasing incidence of NHL

Treatment of Lymphoma

NCI sponsors 80 clinical trials related to adult Hodgkin's disease (of 124 listed in the NCI's PDQ data base) and 22 clinical trials for childhood Hodgkin's disease (of 39 in PDQ). In addition, NCI sponsors 125 clinical trials related to adult non-Hodgkin's lymphoma (of 202 in PDQ) and 34 for childhood non-hodgkin's lymphoma (of 60 in PDQ). Another 39 NCI-

sponsored clinical trials relate specifically to AIDS-related lymphomas. These trials are aimed at improving on existing treatments for lymphomas.

Three types of treatment are most commonly used:

- radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells and shrink tumors)
- chemotherapy (using drugs to kill cancer cells and shrink tumors)
- immunotherapy (treating cancers with monoclonal antibodies or vaccines)

Radiation therapy given to the neck, chest, and lymph nodes under the arms is called radiation therapy to a mantle field. Radiation therapy given to the mantle field and to the lymph nodes in the upper abdomen, the spleen, and the lymph nodes in the pelvis is called total nodal irradiation. Radiation therapy may be used alone or in addition to chemotherapy. Chemotherapy may be taken by pill, or it may be put into the body by inserting a needle into a vein or muscle. Chemotherapy is called a systemic treatment because the drugs enter the bloodstream, travel through the body, and can kill cancer cells throughout the body. To treat certain types of non-Hodgkin's lymphoma that spread to the brain, chemotherapy may be put into the fluid that surrounds the brain through a needle in the brain or back (intrathecal chemotherapy).

Biological treatment tries to help the body to fight cancer or infections. It uses materials made by the body or made in a laboratory to boost, direct, or restore the body's natural defenses against disease. Biological treatment is sometimes called biological response modifier (BRM) therapy. Radioimmunotherapy, which is treatment with a radioactive substance that is linked to an antibody that will attach to the tumor when injected into the body, is also being performed in clinical trials.

Bone marrow transplantation and peripheral blood stem cell transplantation are also being tested in clinical trials for certain patients. NCI spends nearly $70M per year on transplantation research (relevant to numerous types of cancer in addition to lymphomas). Sometimes Hodgkin's disease becomes resistant to treatment with radiation therapy or chemotherapy. Very high doses of chemotherapy may then be used to treat the cancer. Because the high doses of chemotherapy can destroy the bone marrow, marrow is taken from the bones before treatment. The marrow is then frozen, and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer. The marrow is then thawed and given back to the patient through a needle in a vein to replace the marrow that was destroyed. This type of transplant is called an autologous transplant. If the marrow is taken from another person, the transplant is called an allogeneic transplant.

Another type of autologous transplant is called a peripheral blood stem cell transplant. The patient's blood is passed through a machine that removes the stem cells (immature cells from which all blood cells develop), and then returns the blood to the patient. This procedure is called leukapheresis and usually takes 3 or 4 hours to complete. The stem cells are treated with drugs to kill any cancer cells and then frozen until they are transplanted to the patient. This procedure may be done alone or with an autologous bone marrow transplant.

There are treatments for all patients with childhood lymphoma, and patients can be cured. The most common treatments are radiation therapy and/or chemotherapy, but treatment may be different depending on the stage of the cancer and whether the child has reached full growth. We have discovered that some patients develop another form of cancer as a result of their treatment for Hodgkin's disease; for example female patients who received radiation therapy between the ages of 10 and 16 have an increased risk of breast cancer. Therefore, regular follow-up evaluations are advisable.

In general, patients with AIDS-related lymphoma respond to treatment differently from patients with lymphoma who do not have AIDS. AIDS-related lymphoma usually grows faster and spreads outside the lymph nodes and to other parts of the body more often than lymphoma that is not related to AIDS. Because therapy can damage weak immune systems even further, patients who have AIDS-related lymphoma are generally treated with lower doses of drugs than patients who do not have AIDS.

An exciting approach to cancer treatment is immunotherapy, or treatments in which the patient’s own immune system is coaxed to recognize and eradicate cancer cells. One targeted immunotherapeutic approach that recently has met with exciting success involves the use of monoclonal antibodies, proteins derived from cells found in the body’s own immune system, that attach to the surfaces of cancer cells and deliver a deadly substance directly to them. Based on clinical trial results, two monoclonal antibodies recently have been approved for use in cancer treatment:

Rituxan® for B-cell lymphoma, and Herceptin® for metastatic breast cancer. Clinical trials are underway to determine whether these agents may be used or enhanced to combat other types of cancer. Another type of immunotherapy involves cancer treatment vaccines. NCI is sponsoring more than 70 vaccine therapy trials, including studies on using vaccines to treat melanoma and cancers of the breast, prostate, cervix, kidney, pancreas, and ovary.

Anti-cancer vaccines are a high priority of research for NCI. For the first time, results of a recently completed lymphoma cancer vaccine study conducted by NCI intramural researchers have shown that there is a clear anti-tumor effect in a small group of patients who were vaccinated over the course of five years. Unlike conventional vaccines, which are used to prevent illness, the B-cell lymphoma vaccine represents a therapeutic approach, which seeks to strengthen the body's natural defenses against diseases such as cancer that have already developed. On the basis of these promising results, NCI will launch a large-scale, randomized, phase III clinical trial in the near future to definitively test the experimental vaccine, which is custom-made from patients' own tumors.

In a leading scientific journal published in October 1999, the NCI researchers reported that 18 of 20 patients who were vaccinated against this common blood-cell tumor remain in complete remission an average of four years after vaccine therapy began — and have no evidence of microscopic disease. Prior to vaccination, all of the patients in the phase II study had minimal disease or were in a chemotherapy-induced first remission. Complete molecular remissions were documented, using the high technology tool of polymerase chain reaction (PCR), in 75 percent of patients after vaccination.

To create the vaccine, the researchers fused tumor cells taken from individual patients to antibody-producing mouse cells that act as mini-factories, churning out large quantities of tumor proteins. These proteins were then shed into a tissue culture fluid, from which a particular protein of interest was plucked— in this case a receptor molecule on the outer coating of the immune system's B cells. The receptor molecule is exquisitely specific for this type of tumor because it is an immunoglobulin, and since it is unique to a given B cell, any tumor derived from that malignant B cell will have this [receptor molecule] marker.

The vaccine mixture also included a highly immunogenic carrier protein and an "adjuvant" or immune system booster. Patients received an initial injection, followed by booster shots for four months. In the forthcoming pivotal trial, we hope to enroll 390 patients who have been diagnosed with low-grade follicular lymphoma -- the most common form of this cancer -- at a consortium of several clinical centers in North America, to be announced, as well as at the Warren G. Magnuson Clinical Center at the National Institutes of Health in Bethesda, Md.

The Upcoming Lymphoma PRG

Even with this large ongoing effort, the NCI recognizes that more must be done to combat lymphoma. Accordingly, the NCI Director has determined to convene a Progress Review Group (PRG) in the spring of 2000 to sharpen the focus of its large, site-specific research programs with respect to lymphoma, leukemia, and myeloma. The overall goal of this PRG will be to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities which will need to be addressed in order to make progress in understanding, treating, and ultimately preventing these cancers.

The PRG will meet two to three times to assess NCI's current portfolio, review input from outside experts, gather additional data, prioritize key scientific questions, and develop recommendations for action. In addition, a PRG "Roundtable" will be convened in December 2000 to include approximately 150 leading members of the cancer research and advocacy communities related to lymphoma, leukemia, and myeloma. The Roundtable participants meet in an open forum designed to formulate key scientific questions for the next five to ten years in research and to inform the deliberations of the PRG.

The specific charge given the PRG will be to:

- Identify and prioritize scientific needs and opportunities that are critical to hastening progress against lymphoma, leukemia, and myeloma.
- Review an NCI-prepared portfolio analysis of the current research program.
- Review recommendations from the research community generated through the Roundtable meeting.
- Define and prioritize the research agenda.
- Develop an action plan encompassing both operational and strategic components of the NCI's enterprise, using the current research program as the baseline for recommended actions.

Item

Marine Mammals Research -- The Committee notes the unusually low incidence of cancer in sharks, skates, and rays and encourages basic research through the study of the immune system of these marine animals and the examination of bioactive molecules from shark, skate, and ray cells and tissues that have the potential to inhibit disease processes in humans. (p. 68)

Action taken or to be taken

Due to public interest in the potential anti-cancer activity of shark cartilage the NCI is collaborating with NCCAM to sponsor clinical trials in this area. The NCCAM will soon publish a Request For Applications (RFA) for alternative medicine centers with a focus on the topic of cancer. Through this RFA, the NIH and the NCI will welcome applications with an alternative medicine focus on cancer. Currently, the University of Texas M.D. Anderson Cancer Center, which was supported by NCCAM and NCI, and the North Central Cancer Treatment Group have been selected to perform clinical trials to assess the anticancer activity of two oral shark cartilage products. These trials are expected to begin accrual of patients in early calendar year 2000.

Additionally, NCI continues to emphasize its support of the extramural community and investigator initiated research. NCI welcomes the submission of applications focused on this area of research and will continue to support high quality science. Also, NCI supports the public and physicians interested in the potential use of shark cartilage for cancer treatment by providing extensive information in this area in the CancerNet and the Physician Data Query (PDQ), two of NCI's web-based educational tools for physicians and the public.

Item

Multiple Myeloma -- Multiple myeloma (MM) is an incurable cancer of the plasma cells of the bone marrow. MM affects approximately 50,000 Americans annually and the five-year survival rate has only increased from 24 percent to 28 percent from 1974 to 1983 respectively. The Committee urges NCI to use all available mechanisms, as appropriate, to: review its MM research portfolio and both enhance its support of promising research and encourage new investigators into the field; convene an NIH-sponsored Consensus Conference to determine the state of MM research, promising opportunities, and make recommendations to NCI for further research; and integrate epidemiological and occupational health research and data gathering activities relevant to MM to learn more about the molecular pathogenesis of the disease and its suspected agents. The Committee also encourages the Institute to enhance research on the skeletal complications of malignancy. (p. 68)

Action taken or to be taken

Multiple myeloma is an uncommon malignancy involving the plasma cells of the bone marrow. It is diagnosed in approximately 11,000 new patients in the United States each year. The average survival has increased only moderately, from $2^1/_2$ years in the 1970s to $3^1/_2$ - 4 years in the

1990s. However, recently, important advances have been made in our understanding of the biology and possible etiology of this disease, as well as in the treatment and supportive care of these patients.

MM is often preceded by an abnormality referred to as MGUS, or Monoclonal Gammopathy of Undetermined Significance. It has been impossible to distinguish MGUS patients who will remain stable from those whose disease will progress to the fatal MM. The NCI-sponsored cooperative groups are evaluating a variety of clinical, genetic, and biological factors in MGUS patients to help sort out these two groups of patients. The eventual goal would be early intervention to prevent the transformation from MGUS to MM.

Although MM is a generally fatal disease, there are 5-10% of patients who live for 10 or more years. Other studies are examining the long-term survivors in an attempt at determining which genetic or immunologic features are associated with a favorable outcome.

The etiology of MM remains unknown. It occurs more often in blacks, who also experience a poorer outcome, for unknown reasons. In 1990, the NCI convened a national meeting to investigate possible explanations for the increased risk and poorer outcome in blacks. While no definite conclusions were reached, additional research was encouraged. Several laboratories have now demonstrated an association between a virus, named HHV-8 (Human Herpesvirus-8) and multiple myeloma. This virus has also been associated with Kaposi's sarcoma (KS) in patients with HIV-AIDS. Since this virus has been associated with the overproduction of blood vessels (angiogenesis) in KS, the bone marrow of patients with MM has been evaluated and found to also have increased angiogenesis. Investigators at the Mayo Clinic and the University of Arkansas have demonstrated a correlation between bone marrow angiogenesis and prognosis in patients with MM. This observation may lead to important new therapeutic approaches.

A major clinical feature of MM is bone involvement, including thinning of the bones, referred to as osteopenia, as well as punched out or lytic lesions. The latter leads to sever bone pain and pathologic fractures. Over the past few years, the use of a new class of drugs, called bisphosphonates, has reduced the frequency of these bone-related events in patients with MM. There is some evidence that the administration of these drugs may not only improve quality of life, but may also have a positive impact on patient survival. As newer and more effective bisphosphonates are developed, they will be incorporated into NCI-sponsored clinical trials.

Patients with multiple myeloma (MM) are not curable with conventional chemotherapy. Various combinations and permutations of standard doses of conventional agents, with or without the use of alpha-interferon, have failed to make a major improvement in outcome. However, in a recent study conducted by the Southwest Oncology Group there was a significant prolongation of survival in those patients who were treated with prednisone maintenance following a response to standard chemotherapy drugs.

High dose therapy with autologous or allogeneic stem cell transplantation is an active area of research in MM. Data from a collaborative group of French investigators suggested that high dose chemotherapy with autologous stem cell transplantation could prolong the survival of patients with MM when used as part of initial therapy. There is currently a larger NCI-sponsored

national randomized study in the U.S. which will be completed early in the year 2000 and which should provide a more definitive answer to this question.

Investigators at the University of Arkansas have developed a concept referred to as "Total Therapy", in which they combine and sequence many of the most effective drugs and combination regimens in the context of double, or tandem, autologous transplants. This program not only includes chemotherapy drugs, but also interferon and, most recently, thalidomide. Preliminary results with this strategy have been promising.

Although high dose therapy with allogeneic stem cell transplantation can cure some patients with MM, it is associated with significant toxicity with a 30-50% mortality. In addition, there remains a significant risk of relapse. Efforts are underway to identify new preparative regimens which could reduce the toxicity and enhance the efficacy of this approach. There has been a great deal of recent enthusiasm for a procedure referred to as a "mini-transplant" or "submyeloablative" transplant. In contrast to a standard BMT, the "mini-BMT" includes a preparative regimen that is sufficiently immunosuppressive to prevent graft rejection, but not as suppressive of bone marrow function, thereby making it less toxic. An advantage of the "mini-transplant" is that it would make BMT available to older persons and those with some impairment in organ function or performance status. In patients with leukemia and lymphoma, this type of BMT has produced interesting results, notably a high degree of engraftment with very little acute graft-versus-host disease. This approach has also been tested in a small number of MM patients, and additional studies are ongoing.

Several investigators are exploring novel methods of reducing the risk of relapse following either autologous or allogeneic BMT. One approach is to induce an immune response in the patient against the MM protein. This research therapy is being conducted at the Dana Farber Cancer Institute and the Fred Hutchinson Cancer Center. Current studies are determining the feasibility of inducing an active immune response against newly identified myeloma antigens, such as DF3 and MUC-1. If this technique is successful it will be brought to clinical trials to eliminate minimal residual disease. In addition, investigators at the Dana Farber are developing a means of generating an immune response against HHV-8.

Investigators at the University of Minnesota are comparing results using umbilical cord blood cells with peripheral blood and bone marrow as sources of stem cells for transplantation. They are also evaluating the potential of interleukin-2 (IL-2) to generate specific killer cells to prevent relapse following autologous transplantation for MM. Sensitive molecular and genetic marking studies are being used to define whether relapse is the result of contamination in the delivered stem cells or residual disease in the patient.

Patients who fail an allogeneic transplant have an extremely poor outlook. Recent studies have suggested that reinfusion of the white blood cells from the previous donor (donor leukocyte infusions, DLI) may generate a graft-versus MM effect that can induce another response which may be durable and which prolongs survival. Further research is directed at identifying the specific cells responsible for the anti-MM effect.

The NCI also funds the International Bone Marrow Transplant Registry which is the largest repository of information of outcomes following transplantation in a variety of diseases including MM. It collects information on approximately 80% of the transplants performed in the U.S. and shares information with international registries. This Registry provides important information which is used to develop future clinical studies and to generate hypothesis for laboratory research.

The NCI has a long-standing program for the development of new and unique drugs to treat patients with MM. Funds are currently being provided to support research to evaluate new drugs as well as to investigate the mechanisms by which the MM cells become resistant to our therapies. The hope is to be able to develop approaches to overcome this drug resistance. New agents which are not cytotoxic, but which induce the differentiation of myeloma cells are also being evaluated. Preclinical data suggest that such drugs may induce programmed cell death, or apoptosis, of myeloma cells by modulating the bcl-2 oncogene. Other promising agents under investigation include retinoids and arsenic trioxide.

One of the most exciting class of drugs are the antiangiogenesis agents. Recent data from a research grant supported by the NCI to the University of Arkansas have shown that more than 60% of patients with MM who have failed other therapies will experience a response to thalidomide, an inhibitor of this angiogenesis process. The NCI is now sponsoring large scale studies to pursue this important clinical observation.

Other avenues of therapeutic research include novel immune based therapies. Several NCI-funded centers are exploring the role of MM vaccine therapy and other ways to generate a patient immune response against the MM tumor which would hopefully lead to its rejection. Other centers are being funded to study the genetics of MM and the influence of a variety of growth factors on the development of this disease.

NCI staff are actively involved collaborating with extramural investigators and the pharmaceutical and biotechnology industries to identify and study new agents. In addition, workshops are being planned to prioritize the most important clinical and laboratory research questions.

The NCI remains committed to improving the outcome of patients with MM through basic and clinical research. The Cancer Therapy Evaluation Program funds 22 research grants which focus on MM with a total budget of approximately $21 million. In addition, the NCI's Cooperative Groups have committees devoted to developing new treatment strategies for and improving the understanding of the biology of MM. Data are being collected on patients of different races and ethnic backgrounds which will hopefully lead to an explanation for the previously observed differences in outcome among these groups.

Additional research is needed to understand the fundamental questions that will lead to continued progress in this field of research. Studies which will help us to better understand the biology and genetics of MM will eventually lead to new innovative treatments with the potential to improve the survival of these patients.

Item

Neurofibromatosis -- Enormous advances continue to be made in research on neurofibromatosis (NF) since the discovery of the NF1 and NF2 gene, including recent discoveries that NF's suppression of *Ras* is involved with learning disabilities and heart disease in addition to cancer. The Committee encourages NCI to strengthen its NF research portfolio through all available mechanisms, as appropriate, including the further development of animal models, natural history studies, and therapeutic experimentation and clinical trials. The Committee urges NCI to continue to coordinate its efforts with other Institutes engaged in NF research and be prepared to report on the status of the NF research program at its fiscal year 2001 appropriations hearing. (p. 69)

Action taken or to be taken

The neurofibromatoses (NF) are genetic disorders that cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. NF is found in every racial and ethnic group throughout the world and affects both sexes equally. The disorders have been subdivided into neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). Other or variant types of the neurofibromatoses may exist, but are not yet fully characterized. At least eighty-five percent are represented by Type I (Von Recklinghausen or classic peripheral neurofibromatosis, with a prevalence of about 1:4,000 live births) and an additional ten percent by Type II (acoustic or central neurofibromatosis, with a prevalence of about 1:40,000 live births). Both NF1 and NF2 are autosomal dominant disorders with nearly full penetrance and both have a high rate of sporadic occurrence--about 30-50%. In both major forms of NF, severity of symptoms can vary greatly. Effects can be severely disabling, mildly disfiguring or can even go undetected.

NF1 is one of the most common genetic disorders, affecting some 100,000 Americans. NF1 is characterized by multiple cafe-au-lait spots and neurofibromas on or under the skin. Enlargement and deformation of bones and curvature of the spine (scoliosis) may also occur. Occasionally, tumors may develop in the brain, on cranial nerves, or on the spinal cord. About 50% of people with NF also have learning disabilities. Although many affected persons inherit the disorder, between 30 and 50 percent of new cases arise spontaneously through mutation (change) in an individual's genes.

More than half of affected children have some signs of NF1 by 2 years of age. Benign tumors (lumps), under the skin or deeper, may appear at any age but especially during adolescence. The tumors, which grow on nerves, are made up of cells that surround nerves and other cell types, and are called neurofibromas. An affected person may have any number of neurofibromas, from none to hundreds. The tumors, which vary in size, may or may not be painful.

Individuals affected by NF1 often develop tumors that are quite rare in the general population. Malignant gliomas of the visual pathway are very rare, but approximately 20% of all patients with NF1 will develop a visual pathway glioma. Approximately 15 percent of people who have NF1 develop neurofibrosarcoma, an otherwise rare tumor, and approximately 4% of patients with NF1 develop malignant peripheral nerve sheath tumors, which usually develop after a long

latency; some patients develop multiple lesions. This type of tumor is also very rare in the general population. Systemic compromise in individuals with NF1 typically develops before the age of twenty years. The expression of this disease is highly variable, even within an affected family, ranging from mild inconvenience with normal lifespan to serious and progressive manifestations leading to death as early as the perinatal period.

NF2 is characterized by multiple tumors on the cranial and spinal nerves, and by other lesions of the brain and spinal cord. Tumors affecting both of the auditory nerves are the hallmark. Hearing loss beginning in the teens or early twenties is generally the first symptom. Many people with NF2 develop schwannomas of other cranial or peripheral nerves and less develop other sorts of tumors such as meningiomas and ependymomas. NF2 is characterized by bilateral (occurring on both sides of the body) tumors on the eighth cranial nerve. It was formerly called bilateral acoustic neurofibromatosis or central neurofibromatosis because the tumors, which cause progressive hearing loss, were thought to grow primarily on the auditory nerve, a branch of the eighth cranial nerve responsible for hearing. We now know that the tumors typically occur on the vestibular nerve, another branch of the eighth cranial nerve near the auditory nerve. The tumors, called vestibular schwannomas for their location and for the type of cells in them, cause pressure damage to neighboring nerves. In some cases, the damage to nearby vital structures, such as other cranial nerves and the brainstem, can be life-threatening. Symptoms of NF2 may not begin until after puberty. Hearing loss beginning in the teens or early twenties is often the first symptom. Persons with NF2 have few, if any, cafe-au-lait spots or tumors under the skin. A diagnostic technique called magnetic resonance imaging (MRI) has improved early diagnosis of NF2-related tumors.

A number of NIH institutes, including the NCI, support scientists who are striving to understand the genetic and molecular basis of neurofibromatosis. We now know that the NF1 gene is on chromosome 17, while the gene for NF2 is on chromosome 22. Scientists are using this information to develop precise tests aimed at definitively diagnosing these disorders, even before an individual develops symptoms. Some of the life-threatening complications of NF are amenable to treatment. Therefore, alertness to the common clinical manifestations, as well as a thorough evaluation of potentially affected individuals and their families, close follow-up, and thoughtful genetic counseling are well warranted in this disease.

Researchers have identified the protein products these genes dictate, and are beginning to understand the functions of these proteins. This may lead to the development of drugs to treat some of the symptoms of these disorders. The NF1 gene has been cloned and its structure analyzed. The product of the NF1 gene is a large and complex protein called neurofibromin. One portion of this protein is similar to a family of proteins called GAP (guanosine triphosphatase-activating protein). Scientists have demonstrated that GAP proteins play a significant role in cellular signal transduction pathways including the Ras pathway. The GAP proteins act as switches that regulate the complex chemical interactions and sequences of cell growth. The similarity of the NF1 protein to GAP proteins suggests that the NF1 protein may have a similar switching role in the development of neurofibromas. Scientists theorize that defects in the gene may lessen or inhibit the normal output of its protein and allow the irregular cell growth that may lead to tumor development. In addition to the work on NF1, intensive efforts have led to the identification of the NF2 gene on chromosome 22. As in NF1, the NF2

gene product is a tumor suppressor protein (termed merlin or schwannomin). The exact function of merlin is unknown, but it is highly homologous to a family of cytoskeleton associated proteins including moesin, ezrin, radixin and talin. Basic studies in molecular genetics may lead one day to nonsurgical or pharmacologic treatments aimed at retarding or suppressing tumors associated with the neurofibromatoses.

Significant progress has been made in the development of animal models for the neurofibromatoses. By generating mice whose hematopoietic system is reconstituted with neurofibromatosis type 1-deficient hematopoietic stem cells, NCI intramural scientists showed that NF1 gene loss produces a myeloproliferative disease similar to human juvenile chronic myelogenous leukemia, which is observed at increased frequency in juvenile human NF1 patients. They also identified homeobox genes (Hoxa7, Hoxa9, and a Pbx1-related gene, Meis1) that appear to cooperate with NF1 gene loss in the progression to acute murine myeloid disease. They showed that Meis1 is part of a multigene family with at least two other family members, defining a new family of Pbx-related homeobox genes and two new potential disease genes. Mice heterozygous in the NF1 gene are predisposed to a number of tumor types, however unlike humans, these mice do not develop peripheral nerve sheath tumors. Recently, researchers have discovered that chimeric mice composed in part of NF1 null cells do develop these tumors characteristic of the human disease. It was further discovered that mice carrying germ line mutations in NF1 and p53 develop malignant peripheral nerve sheath tumors supporting a causal and cooperative role for p53 mutations in development of such tumors. An independent research group has found that 100% of mice harboring null NF1 and p53 alleles in cis synergize to develop soft tissue sarcomas between 3 and 7 months of age. These sarcomas exhibit loss of heterozygosity at both gene loci and express phenotypic traits characteristic of neural crest derivatives and human NF1 malignancies. These new mouse models provide the means to address fundamental aspects of disease development and to test therapeutic strategies.

To capitalize on these as well as other new mouse models for human cancers, the NCI has established the Mouse Models of Human Cancers Consortium (MMHCC), assembled from multidisciplinary teams of scientists, who will apply their collective scientific expertise in model design and research on human cancer to derive or refine mouse models of human cancers. The MMHCC members will be relied upon for their judgment about appropriate standards for characterization and validation and their skills at devising and applying innovative approaches or new technologies to advance the field of cancer mouse model research. The models that the MMHCC derives and validates for various aspects of cancer research will be made available to the entire research community and should serve to accelerate the pace of discovery of the genetic and epigenetic factors that underlie the initiation of cancer and define the functions of cancer-related genes that promote tumor progression and metastasis. These models will be valuable as the means to test new therapeutic, preventive, early detection, and diagnostic imaging strategies. As the MMHCC progresses, NCI will ensure inclusion of additional partners from the academic and private sector research communities through the formation of specialized MMHCC forums. Each individual forum will have a narrower focus – for example, genetic technology or prevention models or site-specific models – than the overall Consortium. The addition of forums to the MMHCC will enable the Consortium to capitalize rapidly on discoveries in all facets of cancer research, mouse model research, and relevant technologies, and will augment the expertise of the MMHCC.

NCI also supports several clinical trials being conducted within the NCI's Cooperative Group Program that specifically include children with cancers associated with neurofibromatosis. Of special concern are the brain tumors associated with neurofibromatosis. The NCI's PDQ® database of clinical trials contains information on 63 open trials for childhood neurological tumors. These include 38 NCI-sponsored clinical trials of which 15 are Phase I trials testing new approaches to treatment and 2 are Phase III trials, which represent new therapeutic approaches that are closest to introduction into general medical practice. Seven of these clinical trials are being conducted by NCI scientists at the NIH Clinical Center in Bethesda. Selected NCI-sponsored clinical trials are highlighted here.

One study involves chemotherapy for progressive low grade astrocytoma in children less than ten years old. The primary objective of the study is to compare event-free-survival (EFS) in children who are treated either with a regimen of carboplatin and vincristine (CV) or with a regimen of 6-thioguanine (6TG), procarbazine, CCNU, and vincristine (TPCV). Accrual is limited to children with disease that is progressive after surgery or those whose risk of neurologic impairment with progression is high enough to require immediate treatment. Children with neurofibromatosis who have radiographic diagnosis of chiasmatic-hypothalamic tumor are eligible for the study after tumor progression is documented radiographically.

A phase II study of cyclophosphamide, vincristine, and carboplatin for children with progressive astrocytoma is also underway. The primary objective of this study is to evaluate the response rate of cyclophosphamide (1.2 gm/m2 for 4 courses every 3-4 weeks) in children < 10 years with astrocytoma. The study will also estimate the two-year progression-free survival of a therapy program of cyclophosphamide, vincristine, and carboplatin. Children with neurofibromatosis who have low grade astrocytomas and evidence of progressive disease are eligible for the study.

Another phase II study of neoadjuvant vincristine, ifosfamide, doxorubicin, and G- CSF in children with advanced non-rhabdomyosarcoma soft tissue sarcomas has as its primary objective of the evaluation of the response rate to the combination of these agents in children with newly diagnosed inoperable or metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). The study will additionally provide an estimate of the 2-year survival and EFS of children treated with VID in combination with radiotherapy and/or surgery and will additionally establish a bank of frozen tissue (tumor and peripheral blood) for use in further molecular studies of these tumors. Children with neurofibromatosis are predisposed to develop malignant peripheral nerve sheath tumors (neurofibrosarcomas) and are eligible for this study.

Children with NF1 are at increased risk of developing malignant myeloid disorders and their bone marrows frequently show loss of the normal allele of the NF1 tumor-suppressor gene. While often these cases present as juvenile myelomonocytic leukemia (JMML), myeloproliferative syndrome with monosomy 7 also occurs at a significant frequency. The latter group of patients with neurofibromatosis are eligible for the an NCI-sponsored study that seeks to identify the chromosomal location of the gene on chromosome 7 that is important in the development of leukemia.

NCI is additionally developing perillyl alcohol, an investigational agent which is a hydroxylated analog of limonene that is a major component in many citrus essential oils. This agent is of interest in relation to neurofibromatosis since its mechanism of action involves the ras pathway. A primary biochemical activity of perillyl alcohol is inhibition of post-translational protein isoprenylation. Perillyl alcohol additionally has other biochemical activities, and it is not clear at the present time which of these are most related to the antitumor activity observed in preclinical model systems. While a variety of cellular proteins are modified by the process of isoprenylation that facilitates their association with cellular membranes or proteins, perillyl alcohol appears to selectively inhibit the post-translational isoprenylation of 21-26 kDa cell growth-associated proteins, including the oncogenic protein ras-p21. In addition to antitumor activity in mammary tumors, perillyl alcohol has demonstrated antitumor effects in vivo against pancreatic and liver tumors, and in vitro against neuroblastoma and colon carcinoma.

The primary objectives of the phase I studies are to evaluate the maximum tolerated dose (MTD) and toxicities of perillyl alcohol administered in the various regimens. In addition, the trials will investigate the pharmacokinetics of perillyl alcohol and its metabolites as well as the effect of perillyl alcohol on multiple biologic parameters in serum, plasma, PBLs, and tumor. Other studies will be incorporated to study various biologic correlates, for example, ras protein expression and the degree of inhibition of ras isoprenylation in lymphocytes and tumors; the degree of ras inhibition with toxicity and plasma levels of perillyl alcohol and DHPA; and the effect of perillyl alcohol on ras levels measured in peripheral white blood cells and whether farnesyl protein transferase inhibitory activity is present in plasma.

Since 1987, NCI scientists have conducted clinical studies of patients and families with NF2. This work, which involved collaborators from the NEI, NINDS, NIDCD, and the NIH Clinical Center (CC), has provided a valuable resource for expanding NF2 research. In particular, specimens from these families have been used to confirm the location of the NF2 gene on the long arm of chromosome 22 and to identify and clone it. Evaluation of NF2 patients in these families indicated that clinical manifestations of NF2 are similar among affected members of a family but differ between families, leading to the delineation of mild and severe subtypes of NF2. After the NF2 gene was cloned it was possible to identify mutations in individual families and assess if either the type or site of mutation differed between subtypes.

Comparisons between the underlying germ line mutations in NF2 families and the clinical features of affected family members have shown that, in general, patients with severe NF2 (characterized by the presence of many central nervous system tumors in addition to the characteristic vestibular schwannomas) have mutations that prematurely terminated the NF2 protein. In contrast, patients with few central nervous system tumors usually have mutations that alter individual amino acids in the protein or remove some amino acids but leave the beginning and end of the protein intact. This correlation between severity of disease and protein truncating mutations has been observed in other syndromes resulting from mutations in tumor suppressor genes. Studies linking the types of NF2 mutations with specific clinical findings should lead to a better understanding of the function of different components of the NF2 protein.

Ophthalmologic examinations of patients by NEI investigators showed that certain types of cataracts are a major features of NF2. Less frequent was the presence of abnormalities of the

retina. Both ocular manifestations may be present at birth or shortly thereafter, and may be useful in the early identification of affected individuals in NF2 families. NCI continues to follow NF2 patients from high-risk families and offers DNA testing of asymptomatic family members when the mutation in a family has been identified. Future clinical studies include defining the natural history of vestibular schwannomas and intracranial meningiomas, as well as tumors that develop within the spinal cord of some patients with NF2, and evaluating patients with unusual clinical features. In collaboration with investigators from the Massachusetts General Hospital, both studies will attempt to determine underlying germ line mutations.
It is often the case that the study of relatively rare inherited cancers lead to an understanding of the sporadic (non-inherited) forms of that cancer. This may well be the case with NF. It has long been known that radiation can induce tumors, especially among individuals exposed during childhood. NCI investigators are contacting individuals treated with radiation for benign conditions of the head and neck (usually tonsillitis) in childhood who subsequently developed schwannomas within the irradiated area. DNA will be obtained from paraffin blocks of the radiation-induced tumors, and examined for mutation patterns in the NF2 gene compared with those seen in sporadic schwannomas. This study may provide insights into the mechanism through which radiation causes neural tumors.

Because the neurofibromatoses involve tumors that occur in childhood that may affect cognitive functions as well as hearing and sight, these disorders fall within the purview of a number of institutes within the NIH, and attempts are being made to coordinate the research effort across the NIH. For example, as part of a coordinated NIH effort to expand NF research, the NCI will be participating in a meeting with representatives of the other institutes including NICHD, NIDCD, NEI and NHLBI, and NINDS to discuss the current status of NF research supported by the NIH, as well as to explore the possibility of collaborating on a workshop in the Spring 2000. This workshop will assess the state-of-the-science in NF research and identify research needs and opportunities in the field. It is intended that the proceedings of the workshop will strengthen the scientific basis for issuing grant solicitations directed as stimulating research on the many varied aspects of this complex disorder.

Item

Nutrition Science -- Continuing research to determine the precise role of nutrients in the development or prevention of particular forms of cancer is important. The Committee encourages NCI to use all available mechanisms, as appropriate, including small scale clinical trials emphasizing collaboration between clinical research and molecular genetics, to determine the effects of specific dietary behavior on cancer for patients at risk and establishing biomarkers for these conditions. (p. 69)

Action taken or to be taken

The NCI supports behavior change and communications research to determine effective strategies for increasing fruit and vegetable consumption. In light of this objective, the NCI and its award-winning 5-A-Day Program have conducted extensive consumer research to better understand motivators and barriers to eating more fruits and vegetables. In addition, NCI-supported communications research has provided valuable information on how best to reach

target audiences. For example, NCI has been able to pinpoint areas of opportunity to reach the public when they are most likely to be receptive to health messages and to making a change in their eating behavior. Communications research also has been used to build and expand media outreach in an effort to increase the public's knowledge and awareness of the importance of eating at least 5 servings of fruits and vegetables for cancer control. This research has shed light on a range of issues, including health benefits, accessibility, and cost, and has shaped a variety of program components, from messages reinforced in brochures, campaign theme lines, and media materials to consumer tips and suggestions found in grocery stores. For example, understanding consumer attitudes has provided a solid foundation for information and tips that are found on a World Wide Web site that NCI created in partnership with the Centers for Disease Control and Prevention in 1998. This website (http://www.5aday.gov) is designed to encourage fruit and vegetable consumption and physical activity. It enables individuals to enter their daily consumption and activity, then analyzes the results and provides tailored information. It has been heavily promoted in several media campaigns and has drawn considerable public response. Efforts are currently underway to update the 5-A-Day website and make it more user-friendly and informative to the public.

Since 1991, NCI has conducted yearly surveys to track awareness of the 5-A-Day message. Results show that consumer awareness of the need to eat five or more daily servings of fruits and vegetables has more than quadrupled since the beginning of the program, from 8 percent in 1991 to 40 percent in 1999. However, further research is needed on nutrition-based community interventions and behavioral modification for underserved, minority population groups, as well as on long-term maintenance of dietary behavioral change relevant to cancer control. CD-ROM, the Internet, television, and focused, tailored messages specific to the needs of the individual are currently being explored as means to address these issues.

Studies of community interventions to increase fruit and vegetable consumption also have been very promising. Research to develop and test strategies for increasing fruit and vegetable consumption demonstrated a significant increase in fruit and vegetable intake among specific populations, including work sites, schools, and churches, as well as among participants in supplemental food programs. This research and other research in nutrition and behavior change begin to address critical nutrition-related questions for cancer control.

NCI is committed to supporting the spectrum of research addressing fruit and vegetable consumption for cancer control. The following table provides dollars spent in fiscal year 1998 (actual) and fiscal year 1999 (estimated operating level) on research, communications, and evaluation for the 5-A-Day Program.

Component	**Fiscal Year 1998**	**Fiscal Year 1999**
Research Project Grants*	$ 2,759,000 ***	$ 3,272,000 ***
State Health Agency Research**	500,000	650,000
Communications	922,000	1,050,000
Evaluation	250,000	250,000
Total	**4,431,000**	**5,222,000**

*Investigator-initiated R01s
** Funded by NCI via interagency agreement with the Centers for Disease Control and Prevention
*** (1) Gimme 5--Interactive Multimedia Education
(U. TX M.D. Anderson Cancer Ctr., ended in fiscal year 1998)
(2) 5-A-Day Cafeteria Power Plus Program (MN State Dept. Of Health)
(3) Healthy Eating for a Lifetime Program (U. MD)
(4) CIS Research Consortium-Project 1 (AMC Cancer Research Ctr.)
(5) Motivating Dietary Changes in Churches
(Fred Hutchinson Cancer Research Ctr.)
(6) Weight Control to Prevent Cancer in African Americans
(Memorial Hospital of RI)

Prevention Study of Diet, Vitamin D, Calcium, and Hormones with Respect to Colorectal Cancer

The ongoing Womens' Health Initiative is a prevention study of diet, Vitamin D, calcium, and hormones with respect to colorectal cancer.

Phase III placebo-controlled, randomized trials for the prevention of large bowel polyps are ongoing. One trial randomizes patients with a history of bowel adenoma to 2 different doses of aspirin and folic acid, vs. placebo. A second trial randomizes similar patients to wheat bran fiber vs. calcium carbonate. A third phase III randomized placebo controlled double blind study of celecoxib is ongoing for patients with sporadic adenomatous polyps. A fourth trial randomizes patients with a history of adenomas to DFMO $\pm$ Sulindac.

Several phase II trials in adenomas, the precursor to colorectal cancer, are being carried out. These trials assess the activity of various putative chemopreventive agents (e.g., Calcium and Vitamin D, Folic acid, Aspirin, Piroxicam, Sulindac, Celecoxib, DFMO, phenolic compounds, polyamine depletion, and diet) in preventing polyp formation or progression. The effect of the chemopreventive agent on various biomarkers, such as proliferative index, apoptotic index, COX-2 expression, and genetic abnormalities are also being assessed.

Early Detection Research Network

The NCI has created a multi-institutional Network to develop sensitive and specific biomarkers / reagents for the earlier detection of cancer and risk assessment. The purpose of the EDRN is to establish a scientific consortium of investigators, academic as well as industrial, with resources for basic, translational, and clinical research. The EDRN has four components -- Biomarkers Developmental Laboratories, Biomarkers Validation Laboratories, Clinical/Epidemiologic Centers and the Data Management and Coordinating Center. The Biomarkers Developmental Laboratories will have responsibility for the development and characterization of new or refinement of existing biomarkers; the Biomarkers Validation Laboratories will serve as a Network resource for clinical and laboratory validation of biomarkers, which include technological development and refinement; and the Clinical/Epidemiology Centers will conduct clinical and epidemiological research regarding the clinical application of biomarkers. The Data Management and Coordinating Center will be responsible for coordinating the EDRN research

activities, providing logistic supports for the meetings, and conducting statistical and computational research.

Clinical Nutrition Research Units

In addition, the NCI continues to support two Clinical Nutrition Research Units (CNRUs) with one located at the Sloan-Kettering Institute for Cancer Research and the other located at University of California, Los Angeles. The objectives of these CNRUs are: 1) to provide a unified and coherent, multidisciplinary program in nutrition and cancer prevention and control; 2) to advance basic and clinical research; 3) to upgrade the training in nutrition for medical students, physicians and other health professionals, improving the clinical care of patients at their medical centers and in the general population; 4) and to provide up-to-date, accurate information on nutrition.

The CNRU at the Sloan-Kettering Institute for Cancer Research represents the central mechanism for coordinating the major efforts on nutrition and cancer prevention and control research and outreach of the five participating institutions: Memorial Sloan-Kettering Cancer Center, New York Hospital, Cornell University Medical College, The Rockerfeller University, and The Strang Cancer Prevention Center. The four core laboratories focus on carcinogenesis and nutrition, research methodology and analysis, immunology, and lipids. The following research areas in nutrition and cancer prevention and control, funded through the Pilot/Feasibility component of the CNRU, include: 1) new biomarkers of dietary intake and methods to quantify intake; 2) molecular genetics and molecular biology; 3) nutrient-gene-environmental interactions; 4) interdisciplinary basic and clinical science studies; 5) mechanisms of action of dietary constituents for cancer prevention; and 7) mechanisms of individual variation in response to dietary constituents. The CNRU core grant award also provides research support for a New Investigator.

The CNRU at the University of California, Los Angeles (UCLA) serves to integrate research in genetics, cellular and molecular biology, and metabolism with clinical studies in nutrition and cancer prevention. This CNRU serves as an effective catalyst to increase the level of multidisciplinary approaches to nutrition and cancer prevention research of faculty in many academic units within the UCLA School of Medicine, School of Public Health and six affiliated medical centers (Center for Health Sciences, Cedars-Sinai Medical Center, Harbor-UCLA Medical Center, Martin Luther King Medical Center, West LA VAMC, and Sepulveda VAMC). Clinical nutrition research is also facilitated by the active involvement of two NIH-funded General Clinical Research Centers (GCRC's) at the Center for Health Sciences and Harbor-UCLA Medical Center, each equipped with metabolic kitchens and supporting research laboratories.

Specific objectives of the UCLA CNRU are to: 1) Attract young scientists into the field of nutrition and cancer prevention research, with an emphasis on the facilitation of multidisciplinary research addressing highly relevant issues on the role of nutrition in cancer prevention. This is accomplished through the provision of core laboratory services, funding for pilot/feasibility projects, and providing support to carefully selected junior faculty through the New Investigator Awards; 2) To strengthen the training environment for medical students, house

staff, fellows, nutritional science graduate students, and faculty in the area of nutrition and cancer prevention research; and 3) To enhance the utilization of nutrition for the prevention and control of cancer, through nutrition education of practicing physicians, allied health personnel, and the general public.

These objectives are accomplished via the provision of expert technology and services through core laboratories in Nutritional Biomarkers, with facilities for hormone, micronutrient and fatty acid analysis, cellular/molecular and genetic laboratories, nutrition intervention, dietary assessment and body composition, and exercise physiology; Stable Isotopes, and Statistics. In addition, visiting scientists' programs and seminars are held in conjunction with training programs and research centers to strengthen the research environment in nutrition and cancer prevention.

The CNRUs continue to effectively promote new interactions and multidisciplinary research collaborations, which would not have otherwise occurred, as well as having provided opportunities for the initiation of innovative new directions of research on gene-nutrient interactions and their role in cancer prevention and control.

Item

Ovarian Cancer -- While early detection improves the chances that ovarian cancer can be treated successfully, this type of cancer rarely produces symptoms that would alert women, but rather produces symptoms that are mistaken for other ailments or illnesses. As a result, almost 70 percent of women with ovarian cancer are not diagnosed until the disease is in the advanced stage. The five-year survival rate for these women is 28 percent. The Committee is pleased by the progress that has been made in defining a strategic plan for ovarian cancer, particularly with the creation of a SPORE and encourages NCI to move forward with its implementation. The Committee requests that the Director of the Institute be prepared to give a progress report at the fiscal year 2001 appropriations hearing. (p. 69)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. SEER data indicate that ovarian cancer is the fifth leading site of new cancer cases for women and the fifth leading cause of cancer deaths in women. Over 25,000 new cases of ovarian cancer were diagnosed in 1999 and nearly 15,000 American women were killed by ovarian cancer. An estimated 12,800 cases of invasive cervical cancer were diagnosed in America in 1999 and nearly 5,000 American women died of this disease. Although incidence and death rates have been declining, cervical cancer remains in the 10th most frequently diagnosed cancer in U.S. women, and over 200,000 American women are living having had a diagnosis of cervical cancer.

In FY 1999, NCI expended approximately $44 M on research on ovarian cancer. NCI's research portfolio contains over 250 research projects related to ovarian cancer. To assist in prioritizing research on this disease, the NCI in December 1997 organized a strategic planning meeting in conjunction with the Society of Gynecologic Oncologists and the DHHS Office of Women's

Health. The recommendations from that meeting were published by the NCI in April 1998. In December 1998, the NCI, again in conjunction with the Society of Gynecologic Oncologists and the DHHS Office of Women's Health, organized a follow-up meeting to determine how best to implement the 1997 recommendations.

In accordance with the 1997 recommendations, the NCI advertised for applications to expand the current SPORE program to ovarian cancer. Ten applications were reviewed in spring, 1999. Awards, totaling $5.85 M were made to four institutions in September, 1999. These four SPOREs will be centered at the University of Texas MD Anderson Cancer Center, the Fred Hutchinson Cancer Research Center, the Fox Chase Cancer Center, and the University of Alabama at Birmingham. The projects to be funded focus on translation research on the biology, prevention, evaluation of risk, screening, and treatment.

The NCI has created a multi-institutional network to develop sensitive and specific biomarkers for the earlier detection of cancer (the Early Detection Research Network). One component of this network is a consortium of research centers which will work together to identify better markers for ovarian cancer. About $1.5 M has been awarded for biomarkers research focusing on earlier detection of ovarian cancer.

The Cancer Genome Analysis Project (CGAP) continues to utilize the newest technologies to identify and characterize the genes of normal, precancerous and malignant ovarian tissue. Currently, nearly 1700 genes unique to ovarian tissue have been isolated from normal and cancerous tissues. All information from CGAP is available to researchers for studies leading to an understanding of the mechanisms of the development and progression of cancer. Some of these unique genes may be useful as markers for early detection, prognosis, and/or progression.

The PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial, begun in 1991 and continuing for 16 years, studies whether certain screening tests are effective in the early detection of specific cancers. For ovarian cancer, the researchers are testing whether using a blood test for the tumor marker known as CA-125 and transvaginal ultrasound will decrease the number of deaths from the disease.

The NCI has also organized a working group on ovarian cancer screening which will bring together US and international experts who will meet every six months to review new developments in imaging and markers, as well as data from the ongoing PLCO screening trial. As progress in imaging and markers is made, this working group will be able to design follow-up phase III trials as appropriate.

The NCI has organized a working group on cancer genetics for women with BRCA1 and BRCA2 mutations that increase a woman’s risk for breast and ovarian cancers. This group brings together representatives of the Cancer Family Registries and the Cancer Genetics Network with representatives of the Clinical Trials Cooperative Groups and the Society of Gynecologic Oncologists. The goal of the working group is to develop prospective cohort studies and clinical trials to help identify interventions which can reduce the risk of developing breast or ovarian cancer, help these women make decisions on reproductive issues, such as child-bearing and the

use of hormonal replacement therapy, and help delineate the contributions of environment, reproductive health, and genetics upon the risk of developing cancer.

Clinical Trials Cooperative Groups in the United States, Europe, and Australia have established the Gynecologic Cancer Intergroup (GCIG). This committee, which meets every six months, helps coordinate phase III clinical trials in ovarian and other gynecologic malignancies. Investigators from the US are working with doctors from the United Kingdom, Italy, and Denmark to plan a large, 4000-patient trial for women with ovarian cancer. As currently designed, this trial will evaluate the role of two new drugs, gemcitabine and topotecan, as well as a new formulation, liposomal doxorubicin, in the primary treatment of women with advanced ovarian cancer.

The NCI is also working with the Clinical Trials Cooperative Groups and the NCI-designated Cancer Centers to evaluate and improve quality of life among ovarian cancer patients and survivors. The Office of Cancer Survivorship, within the Division of Cancer Control and Population Science, has a particular focus on these issues.

The Director's Challenge initiative supports the application of powerful new technologies to the analysis of molecular changes in human tumors (molecular profiles). The initiative challenges the scientific community to develop new tumor classification systems based on the patterns of these molecular changes. These molecular profiles will complement the current morphology-based tumor classification systems which often are not able to distinguish patients with tumors that appear to be similar but who will have very different clinical outcomes. Knowing the molecular changes that have taken place in individual tumors may allow physicians to make more effective management decisions for patients.

Two research projects developing molecular profiles for ovarian tumors were supported in the first round of funding of the Director's Challenge initiative. Significant variation exists in the classification of ovarian tumors based on morphological features. This variation makes effective management of individual ovarian cancer patients difficult. Both research projects will develop molecular profiles that correlate with the degree of malignancy and the outcome for the patients with the most common type of ovarian tumors. These molecular profiles may allow physicians to select the most effective therapy for individual patients. In addition to the primary focus, one of the projects will develop molecular profiles that identify patients who will respond to platinum based therapies. The investigators also anticipate that, based on the molecular profiles, potential new molecular targets for therapy will be identified. The second project will attempt to identify molecular profiles that distinguish the four major categories of ovarian tumors and molecular profiles that may help identify precancerous lesions of ovarian tumors. Molecular profiles that identify precancerous lesions may be critical for developing strategies to detect ovarian cancer earlier.

At least five new applications proposing development of molecular profiles in ovarian cancer are expected to be submitted for the second round of the Director's Challenge initiative.

Item

Pancreatic Cancer -- Pancreatic cancer is the fourth leading cause of cancer deaths for men and women in the United States. Typically not diagnosed until it has reached advanced stages when treatment options are limited and largely ineffective, the five-year survival rate for people with pancreatic cancer is only four percent. The Committee requests NCI to submit a report, by January 31, 2000, which details the Institute's plan to enhance its support for pancreatic cancer research and education efforts. (p. 69)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Cancers of the digestive system claimed 131,000 American lives last year with 226,300 new cases diagnosed. The largest number of these new cases (129,400) and deaths (56,600) were associated with colorectal cancer. Other leading gastrointestinal cancers include: pancreatic cancer (28,600 new cases and 28,600 deaths); stomach cancer (21,900 new cases and 13,500 deaths; liver and intrahepatic bile duct cancer (14,500 new cases and 13,600 deaths); and esophageal cancer (12,500 new cases and 12,200 deaths)

An estimated 28,600 new cases of pancreatic cancer were diagnosed in the United States in 1999. Although the incidence rates of pancreatic cancer in men have declined over the past 20 years, the incidence rates in women have remained approximately constant. Similarly while death rates in men have decreased by about 1% per year lately, the mortality rate from pancreatic cancer in women has increased slightly. The NCI expended approximately $15.5 million in fiscal year 1999 on pancreatic cancer and supports over 100 research grants related to pancreatic cancer. Even with this ongoing effort the NCI is desirous of funding more research on pancreatic cancer. To set priorities for this research, the NCI Director is convening a Pancreatic Cancer Progress Review Group (PaCPRG) in the Spring of 2000 to sharpen the focus of its large, site-specific research programs with respect to pancreatic cancer. The overall goal of the PaCPRG is to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities which will need to be addressed in order to make progress in understanding, treating, and ultimately preventing pancreatic cancer.

Several investigator initiated studies have been funded, which study genetic predispositions to cancer (such as the tumor suppressor gene DPC4, a target of 18Q homozygous deletions, which are present in 90% of pancreatic cancers, and the mucin MUC4), as well as discovery of secreted proteins, which may be diagnostic of pancreatic cancer. SPOREs are concentrating on finding new genetic markers for pancreatic cancer. The Biomarker Developmental Laboratory grants from the Early Detection Research Network funded a laboratory which will perform detailed mutational analysis of specific genes using a variety of technologies, and develop new technologies which can quantify point mutations at the cytologic level in pancreatic fluids.

In previous solicitations for gastrointestinal SPOREs in 1992 and 1996, NCI requested that at least one project of the SPORE should be in pancreatic cancer. Two SPOREs were funded in the second solicitation and one of them, from the University of Nebraska was entirely focused on pancreatic cancer. For the other funded SPORE (Johns Hopkins University), 50% of the research is dedicated to pancreatic cancer. Together, these two projects represent about $3.5 million total costs dedicated to pancreatic cancer research. Both SPOREs have significant developmental therapies and early diagnosis and detection research activities.

In addition to surgery, three types of treatment are most commonly used in cancer treatment:

- Radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells and shrink tumors)
- Chemotherapy (using drugs to kill cancer cells and shrink tumors)
- Immunotherapy (treating cancers with antibodies or therapeutic vaccines)

All three of these approaches are being used in NCI-sponsored clinical trials for patients with pancreatic cancer. The NCI's PDQ database contains over 180 trials open to patients with pancreatic cancer. Of these, 125 are NCI-sponsored including 94 Phase I trials in which new interventions are being tested for safety and 5 Phase III trials representing treatments that are closest to introduction into general medical practice.

Drugs used in chemotherapy use different ways to stop tumor cells from dividing so they stop growing or die. Radiation therapy uses high-energy x-rays to damage tumor cells. Combining radiation therapy with chemotherapy may kill more tumor cells. It is not yet known which treatment regimen is most effective for pancreatic cancer. One NCI-sponsored randomized phase III trial seeks to compare the effectiveness of fluorouracil and gemcitabine plus radiation therapy in treating patients with cancer of the pancreas who have undergone surgery.

Surgery to remove the pancreas, some of the small intestine, and lymph nodes may be more effective treatment for cancer of the pancreas than surgery to remove the pancreas and some of the small intestine alone. Combining surgery, radiation therapy, and chemotherapy may be an effective treatment for cancer of the pancreas. Another NCI-Sponsored randomized phase III trial aims to compare the effectiveness of surgery to remove the pancreas and a portion of the small intestine with or without removing lymph nodes, followed by radiation therapy and chemotherapy, in treating patients with cancer of the pancreas.

The NCI has provided administrative support to allow the National Center for Complementary and Alternative Medicine (NCCAM) to begin a large prospective evaluation of a nutritional program with oral pancreatic enzymes and a "detoxification" regimen at Columbia Presbyterian Medical Center, one of the NCI designated Cancer Centers. This clinical trial will compare this alternative medicine designed regimen to conventional chemotherapy for patients with advanced pancreatic cancer. The protocol is open to patient accrual and is advertised on the NCI's Physicians Data Query (PDQ).

The NCI is in preparation to build a long-range plan for pancreatic cancer research and education efforts. The NCI Director previously scheduled and will convene a Pancreatic Cancer Progress

Review Group (PaCPRG) in the Spring of 2000 to sharpen the focus of NCI's large, site-specific research programs with respect to pancreatic cancer. The overall goal of the PaCPRG is to develop a national plan based on a description of ongoing scientific activities and investigations, and a prioritized list of the scientific needs and opportunities that will need to be addressed in order to make progress in understanding, treating, and ultimately preventing pancreatic cancer. The PaCPRG will likely submit its final report at the end of the year 2000 with the subsequent NCI response to the PRG report expected in the Spring of 2001.

The PaCPRG will meet two to three times to assess NCI's current pancreatic cancer portfolio, review input from outside experts, gather additional data, prioritize key scientific questions, and develop recommendations for action. In addition, a PRG "Roundtable" will be convened in the Fall of 2000 to include over 150 leading members of the pancreatic cancer research and advocacy communities. The Roundtable participants meet in an open forum designed to formulate key scientific questions for the next five to ten years in pancreatic cancer research and to inform, expand and focus the deliberations of the PaCPRG. The specific charge to be given to the PaCPRG is to:

- Identify and prioritize scientific needs and opportunities that are critical to hastening progress against pancreatic cancer.
- Review an NCI-prepared portfolio analysis of the current research program.
- Review recommendations from the research community generated through the Pancreatic Cancer Roundtable meeting.
- Define and prioritize the research agenda.
- Develop an action plan encompassing both operational and strategic components of the NCI's pancreatic cancer enterprise, using the current research program as the baseline for recommended actions.

Members of the PaCPRG, representing basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community will work together to develop a broad, multidisciplinary perspective of ongoing pancreatic cancer research. This group of experts, using input from the scientific community and a comprehensive report of the NCI's pancreatic cancer research portfolio, will identify and prioritize scientific needs and opportunities critical to advancing the field in the next five to ten years.

Item

Primary Immune Deficiency Diseases -- The Committee is pleased to learn that NCI will participate in a symposium, in conjunction with the Office of Rare Diseases, NICHHD, NIAID, and NHGRI, to investigate the relationship between primary immune deficiency diseases and cancer with the goal of identifying areas of scientific research that can be enhanced through appropriate funding mechanisms. The symposium will bring together leading national and international experts in cancer, pediatrics, immunology, and genetics. The Committee looks forward to reviewing the report of the symposium prior to the fiscal year 2000 appropriations hearing. The Committee also supports NCI's interest in the creation of a trans-Institute intramural clinic for the diagnosis of immune deficient patients. (p.69)

Action taken or to be taken

The NCI, in collaboration with the NIAID and NHGRI, has scheduled a symposium to convene in March 2000 on the relationship between cancer and primary immune deficiency diseases. The purpose of this symposium is to bring together experts in the fields of cancer, genetics and immunology to share their insights into the etiology of cancer in immunodeficient patients. The ultimate goal is to focus on areas of scientific research that can be enhanced through appropriate funding mechanisms. The timing of this symposium was delayed from late 1999 to early 2000 to allow for a more comprehensive gathering of interested parties.

The primary immune deficiency diseases result from innate genetic mutations in the immune system that occur in utero. This type of immunodeficiency puts patients at high risk for severe infections and the development of malignancies. In addition, several autoimmune syndromes have been described in association with immune deficiency diseases. The study of the genetic and molecular basis of these disorders has not only been of great importance to the affected patients but has been of great value in providing insights for immunologists plus extending our understanding of the genetic mechanisms that underlie autoimmune disease and cancer. Progress in both clinical immunology and in the field of primary immune deficiency diseases has been extremely rapid. Forty-six years ago, in 1953, at the time of the opening of the NIH Clinical Center, the function of the lymphocyte was obscure and there was no definition of the two pathways of the specific immune system, one involving antibodies and the other cellular immunity. In subsequent years, the field of immunology, because of research supported by extramural NIH grants and that performed by patient-oriented clinical researchers in the NIH Clinical Center, has undergone a revolution from a largely phenomenological science into a deeply analytical and highly technological discipline. The primary immune deficiency diseases functioning as experiments of nature, in both humans and animals, have played pivotal roles in stimulating scientific inquiry and providing incisive questions which can be taken from the clinic to the laboratory for definitive analysis. The examination of these patients has led to the development of techniques to study the human immune response and its defects; the distinction of more than 80 primary immune deficiency diseases, the definition of 75 genes whose abnormalities lead to primary immune deficiency diseases, as well as the introduction of such therapeutic approaches as the infusion of gammaglobulin, missing enzymes and bone marrow transplantation.

Within the intramural NIH community, a series of interest groups have been established that concern the primary immune deficiency diseases including groups focusing on fundamental immunology, clinical immunology and gene therapy. Furthermore, a common diagnostic research laboratory is being established to provide in vitro studies for the optimal evaluation of patients with immune deficiency disorders. This diagnostic laboratory would be funded by a competitive application to the NIH Clinical Center. Space as well as other resources would involve investigators from the Clinical Center NIH, NCI, NIAID, NIAMS, NHLBI and NHGRI. This initiative might ultimately lead to the establishment of a trans-institute clinic for the diagnosis and treatment of immune deficiency patients. This may become an opportunity to create a national and international resource where investigators might come to the NIH along with their patients and participate in the clinical and laboratory investigation of their patients. Further, efforts are being made to establish repositories of human cell lines from

immunodeficient patients and repositories of frozen embryos from relevant immunodeficient mouse models. In addition, intramural scientists are active in a number of national and international organizations with a special interest in primary immune deficiency diseases. They are major participants in the scientific advisory boards of PAGID, the Pan American organization dedicated to the study of primary immune deficiency diseases, the Jeffrey Modell Foundation, the International Organization for Primary Immunodeficiency Diseases (IPOPI), and in the NIAID Task Force on Immunology. Finally, from its inception three decades ago, select intramural NCI scientists have been active as members of the World Health Organization (WHO) scientific group on primary immune deficiency diseases that has organized semiannual meetings on these disorders.

Both cancer and primary immunodeficiencies, two human diseases, share a common cause - genetic mutations. In addition, cancer and primary immunodeficiencies are further related because those children, as well as adults, who are immune deficient, are at high risk for developing cancer, particularly cancers of the dysfunctional immune system. The cancer frequently detected in these patients is Non-Hodgkins lymphoma (NHL). NHL occurs in a population of lymphocytes that normally are responsible for resistance to infectious disease, but for some reason, become malignant. Examples of primary immune deficient patients who are a high risk for developing NHL are patients diagnosed with Wiskott-Aldrich syndrome (WAS), Ataxia-telangiectasia and Autoimmune Lymphoproliferative (ALPS) disease. However, the exact cause of how cancer arises in primary immune deficient patients is not known. To facilitate the most promising areas of research and develop a comprehensive agenda for research initiatives in this area, the previously mentioned symposium, on the relationship between cancer and primary immune deficiency diseases, is scheduled to convene during March 2000.

Item

Prostate Cancer -- Cancer of the prostate is the most commonly diagnosed nonskin cancer in America. If detected early, it can be treated successfully with no negative impact on the cancer survivor's quality of life. However, existing forms of detection are insufficient, and available treatments frequently result in erectile dysfunction, urinary problems, or other disorders and disruptions that do negatively impact the patients quality of life. The Committee urges NCI to place an increased priority on research through all available mechanisms, as appropriate, including clinical trials, that will result in earlier, more reliable detection methods and more effective and less disfiguring treatment regimes. The Committee commends NCI and other NIH Institute Directors for the five-year investment strategy for prostate cancer research and encourages its implementation. (p.70)

Action taken or to be taken

The nature and magnitude of the burden of prostate cancer has been tracked by the National Cancer Institute’s surveillance program, and we estimate that about 180,000 men will be newly diagnosed with prostate cancer this year and about 37,000 will die. Prostate cancer exacts a particularly devastating toll on African American men; incidence rates are substantially higher among African Americans, and mortality rates in African American men remain more than twice as high as rates in white men.

This catalogue of statistics, while accurate, does little to convey the pain, fear, and uncertainty experienced by every man who is diagnosed with prostate cancer. Despite advances over the past decade, our treatments for prostate cancer are not adequate, the side effects of treatment are significant and often unacceptable, and troubling questions remain about the efficacy of early detection for the disease. Every day, too many men in the United States hear the life-changing words "You have prostate cancer." Every day, too many men are faced with the agonizing decisions of how best to treat their prostate cancer. And every day, too many men are dying too young of this disease. The limited knowledge about the causes of prostate cancer, how it may be prevented, and how to treat it successfully demand a broad, robust, and clearly articulated and robust approach to research.

The National Cancer Institute (NCI) has been increasing substantially its support for all types of studies relating to prostate cancer. We wish to speed the generation of new insights into the biology and behavior of this common tumor and increase the rate at which new insights are translated into more effective interventions for prevention, detection, diagnosis, and treatment.

The NIH plan for a coordinated, trans-NIH prostate cancer research initiative was outlined in *Planning for Prostate Cancer Research: Five Year Professional Judgment Estimates* and found at the web site address http://www.nci.nih.gov/prostateplan.html. This 5 Year Plan was provided to Congress in 1999. The report describes prostate cancer research opportunities across NIH from 1999 through 2003. The NCI is the lead NIH institute for prostate cancer research. Ongoing and future research initiatives have the potential to directly improve the length and quality of life of prostate cancer patients and survivors, as well as those at risk for the disease. Indeed, fully 70 percent of the research opportunities presented here are targeted at clinical or translational research that would have a direct impact on patients, survivors, and at-risk men. At NCI, prostate cancer research funding increased significantly from a 1998 level of $86.9 million to a current projection of $135 million in 1999.

The NCI has aggressively sought participation from non-government researchers, advocates, and patients in reviewing the prostate cancer research portfolio and charting a plan for a vigorous expansion of the prostate cancer research program. Over two years ago, we initiated a disease-specific planning process called a progress review group or PRG. The Prostate Cancer PRG involved scores of individuals from all over the country -- scientists, clinicians, and advocates -- and challenged the prostate cancer research community and the NCI to review our current prostate cancer research portfolio, to develop a prioritized set of questions that needed to be answered and resources that needed to be developed or applied, and provide a vision to chart a course for research and progress in prostate cancer. In all of the planning phases NCI made an effort to involve a variety of members of the prostate cancer communities including researchers, clinicians and advocates. To ensure that the professional and advocacy groups were fully represented, the PRG invited the input of 32 "stakeholder" groups that represented both professional societies and advocacy organizations and groups. The PRG report was presented to the NCI in September 1998 and in the time since then NCI has acted to implement a plan that we believe will fulfill the vision of progress articulated by the PRG.

NCI has begun, in an aggressive way, to accelerate funding for prostate cancer:

- We have identified more than 20 initiatives through which high priority areas can be addressed and a special section of the NCI Web site serves to bring these to the attention of researchers and the public. These may be found at web site http://www.nci.nih.gov/prostate.html.
- We have further emphasized the importance of accelerating the pace of progress against prostate cancer by promising applicants that prostate cancer grant applications will have priority for so-called exception funding. That is, every effort will be made to fund worthy applications in the identified high-priority research areas even when peer-review assigned priority scores are not quite high enough to fit within conventional grant award paylines.
- NCI has met with the representatives of the prostate cancer research community, the PRG, and the leadership of professional societies, such as the American Urological Association, in order to communicate these initiatives and to enlist the research community's support in responding to these opportunities.
- Extensive outreach and advertising have been developed to alert the larger research community to these opportunities to energize their participation in this prostate cancer research program.

The scientific opportunities we have identified fall into four major areas:

- Clinical Science -- the near term direct testing of new interventions in patients or in those at risk for prostate cancer.
- Translational Science -- moving ideas from the laboratory to the point of clinical testing, and determining how they should be applied and tested.
- Risk, Burdens & Outcomes Science -- attempting to ask critical questions about cause, the unequal levels of cancer in different populations, outcomes and survivorship.
- Basic research and discovery -- longer term investments in gaining insight into the development and biology of prostate cancer and the development of models for study.

A few examples may help to explain some of these new initiatives:

The first stages in therapeutics development are notoriously complex and NCI has developed a series of initiatives to expedite this process. Called Rapid Access to Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID), these new programs create a drug development process that enables investigators to advance novel molecules to begin clinical trials when they have not yet found a pharmaceutical or biotechnology industry partner with the necessary resources. We do this by giving academic investigators access, on a competitive basis, to NCI's preclinical drug development resources and expertise. Investigators who have molecules that hold promise for cancer treatment, but without access to the development resources required for initiation of clinical studies, are invited to submit applications twice a year. Those selected for support are assisted with necessary development steps to enable Investigational New Drug Application (IND) filing with the Food and Drug Administration and to begin initiation of proof-of-principle clinical trials. For FY 2000, our goal is the development of three to five new therapeutic agents, each relevant to prostate cancer. Projects already approved in 1999 include development of a bioreductive compound with potential as a radio- and chemo-sensitizer, and a gene-therapy approach that will

convert inactive pro-drugs into toxic agents within prostate cancer cells. Over five years, 15 new therapeutic agents for prostate cancer could potentially be developed if sufficient resources are available.

The next step is testing new approaches and new agents aimed at a variety of clinical situations in initial clinical trials for patients with prostate cancer. NCI has established Prostate Cancer "Quick Trials", a new granting program providing a rapid, streamlined, funding mechanism for moving novel ideas for therapeutic interventions into Phase I and Phase II clinical trials for prostate cancer. This program has been set up in recognition of the urgent need for new types of interventions that are effective at different stages of prostate cancer, as well as the growing number of therapeutic ideas being developed by academia and industry that are ready to be tested in patients. In this type of project, where it is necessary to evaluate untested leads in the absence of preliminary data, conventional grant application and review procedures are not well suited. Quick Trials utilizes a process for rapid approval of early clinical trials. In addition, although there was little time in advance of the first submission date for applicants to familiarize themselves with the new Prostate Cancer Quick Trials initiative, twelve applications were received in the first round and 3 of these were funded in FY 1999.

The agents to be evaluated were:

- A new lytic, replication-competent adenovirus (Ad5-CD/TKrep) to selectively deliver a pair of therapeutic "suicide" genes to prostate tumors (this agent was developed to this stage via the RAID mechanism)
- An oral Vitamin D derivative that may avoid the hypercalcemia that has thus far precluded a therapeutic role for vitamin D in prostate cancer
- 17-N-allylamino-17-demethoxy geldanamycin (1 7-AAG), the first in a new class of compounds that induce the selective degradation of proteins which bind to the Hsp90 family of chaperone proteins that play key roles in cell cycle control. Malignant cells that express the androgen receptor (AR) and which overexpress cyclin D1, as do many prostate cancers, are sensitive to these agents.

The NCI's goals are to increase the number of patients participating in early clinical trials by two to three-fold and to initiate 10-15 new trials per year through this accelerated mechanism. In FY 1999, eight new phase I/phase II prostate cancer trials of Cancer Therapy Evaluation Program (CTEP) sponsored agents were activated with another nine new phase I/phase II prostate cancer trials of CTEP-sponsored agents reviewed and close to activation. Also, there were 21 new solid tumor phase I trials of CTEP-sponsored agents that may enroll prostate cancer patients activated in FY 1999 and another 20 new solid tumor phase I trials of CTEP-sponsored agents that may enroll prostate cancer patients in review and nearing activation by the end of FY 1999. In addition, in FY 2000 through NCI's Cancer Therapy Evaluation Program, NCI will initiate approximately 35 new Phase I/II trials in Prostate Cancer with agents directed against a number of particularly promising molecular targets and mechanisms. These targets include:

- Angiogenesis and metastasis, the processes by which cancers induce new blood-vessel formation, invade these blood vessels, and spread throughout the body;
- Growth factors and their receptors, which mediate growth signals to cancer cells; and

- Tissue-specific genes expressed selectively in prostate or prostate cancer cells, thus allowing for the targeting of tumor-killing modalities to these cells.

Compared to the current level of effort, this plan could more than double the number of early clinical trials in prostate cancer in the first year, with another doubling projected in the next four years as per the full professional judgment estimate presented to Congress by Dr. Klausner in June 1999.

In addition to these early stage trials of new treatments, NCI will support an expanded program of new multi-center phase III clinical trials in prostate cancer. A number of major changes in the NCI's clinical trials infrastructure are anticipated to lead to a doubling in the number of these phase III studies in the next several years. These are studies aimed at determining definitively which treatments can be shown to offer genuine benefits to patients and what should be considered the current optimal therapies for various stages of the prostate cancer. For instance, such studies will explore the relative utility of different treatments, such as prostatectomy and brachytherapy ("seed implant") for initial management, and new hormonal and chemotherapeutic approaches for the most common clinical presentations of the disease, including:

- Adjuvant therapy in the setting of primary surgical or radiation treatment
- Neo-adjuvant therapy, which has shown promising results in reducing the mortality from locally advanced prostate cancer
- Treatment after hormone therapy
- Treatment in the setting of rising PSA levels after definitive local therapy
- Advanced disease, particularly directed at bony metastases

The NCI is also moving quickly in important directions to develop complementary and alternative medicine (CAM) information and expand research opportunities for CAM investigators. These activities are broad in scope and include strengthening the relationship with the National Center for Complementary and Alternative Medicine (NCCAM), the careful evaluation of CAM therapies, and the development of accurate CAM information for the public. Recently, Requests for Applications (RFA) have been issued by NCI in conjunction with NCCAM and other Institutes. The intent is to establish Centers for CAM Research that would provide the resources necessary for the rigorous scientific study of CAM approaches, as well as Specialized Research Centers to investigate the biological effects of botanicals, including those that are available as dietary supplements. Selections for Center sites are anticipated this fall.

Several studies of CAM approaches are already underway. NCI - sponsored projects recently have suggested that both vitamin E and selenium supplements can safely prevent prostate and other cancers. More investigation is indicated and NCI continues to support several studies addressing effectiveness in the prevention of prostate cancer by lycopene and dietary soy, as well as vitamin E and selenium.

A number of additional central questions about prostate cancer have been identified, as well as potential strategies to address them. These include:

- Testing promising preventive agents, particularly in high risk individuals

- Developing new predictive molecular diagnostics
- Validating current and new early detection markers
- The linkage of new imaging technology to directing therapy and assessing its effects without invasive procedures
- Epidemiologic studies to attempt to systematically identify correlates of the profound geographic and population differences in prostate cancer rates
- Developing new animal models that faithfully reproduce human prostate cancer in order to better understand tumor development and spread, and to better test preventive and therapeutic interventions

All of these opportunities build on a strong base of existing prostate cancer research including:

- Animal Models. NCI is currently soliciting applications for the establishment of a consortium that will develop and validate murine models for human cancer. The existence of models that truly reflect the behavior of human cancer and its responsiveness to preventive and therapeutic maneuvers would have a profound effect on our ability to understand the process of malignant transformation and to develop interventions to prevent or treat it. Prostate-cancer investigators have already had a measure of success developing improved animal models. NCI has also issued a call for grant supplements from investigators interested in developing mouse models for human cancer as an extension of the approved content of their grant. Additional supplements for other model systems, including the dog, which may be of particular relevance to prostate cancer, can be considered on an individual basis.
- The Cancer Genome Anatomy Project (CGAP), the goals of which are to build an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. The tumor type with the highest representation in the early stages of the CGAP effort is prostate cancer. NCI has facilitated investigator collaborations of interdisciplinary studies following the recent discovery of a susceptibility gene on chromosome 1. Leads from this effort may help to clarify genetic and gene-environment interactions responsible for black-white differences in risk.
- The Cancer Chromosomal Aberrations Project and the Genetic Annotation Initiative, which seek to integrate the chromosome, gene, and physical maps of the human genome and provide a resource to researchers comparing this information to what can be determined about tumors from examination under the conventional microscope.
- Other initiatives supporting the development of technologies for high-throughput molecular analysis of the changes associated with cancer and the development of full-length libraries of genes expressed in cancers.
- Together, these initiatives feed into the Director's Challenge for Molecular Diagnostics: The NCI Director has recently challenged the research community to revolutionize our classification of human tumors. The classifications of diagnostic pathology have always been on a morphological basis and often carry little information about tumor behavior, prognosis, and sensitivity to treatment. It is now time to combine technological advance in molecular detection with rapidly advancing knowledge of tumor biology in a manner that will provide more sophisticated classification of cancer based on molecular criteria. Nowhere is this need greater than in prostate cancer. Despite the impressive prevalence of apparently malignant change in the prostates of asymptomatic men, these morphological abnormalities do not

always signify aggressive clinical behavior. We are currently unable to predict accurately which patients should be treated aggressively and which may be followed expectantly.

- Early Detection Network**.** The NCI intends to establish a multi-institutional consortium to develop sensitive and specific tests for the early detection of cancer. This Network will link centers of expertise in tumor biology, diagnostics technologies, and clinical-trials methodology in academia and industry to develop high-throughput assays suitable for clinical testing. The Network will have the capacity to establish estimates of the operating characteristics of candidate assays as early-detection tools. NCI intends that prostate cancer should be one focus of activity within the new Network, and the great current interest in the prostate-specific antigen (PSA) shows the feasibility of this approach. To expedite the discovery and development of more sensitive and specific markers for early disease, NCI will also establish links between activities of the Network and programs in academia and industry that are developing libraries of all known secreted proteins in mammalian cells.
- Cancer Genetics Network. This recently organized multicenter consortium is a platform for studies of genetic susceptibility. It will serve as a vehicle for gene discovery and is creating a registry of individuals at high risk for cancer. These individuals may serve as probands for the identification of families or as participants in other types of studies of cancer susceptibility. The Network will provide registry participants with relevant information about cancer predisposition and will facilitate access to studies focused on early detection and prevention. This year the Network is implementing pilot projects, recruiting participants into the registry, and developing operating procedures. The Network is planning activities to publicize the procedures by which the research community may gain access to its resources.
- Diagnostic Imaging. The NCI has recently funded a national multi-institutional network for cooperative studies in diagnostic imaging. This Network will develop productive interfaces with industrial sources of new imaging technology and will have the capacity to perform both limited-institution pilot studies and full-scale randomized controlled trials to assess the value of imaging innovations in the practice of oncology. NCI expects that studies in prostate cancer will form an important part of the research agenda of this network, aided by collaborative arrangements with the clinical cooperative groups. NCI recently announced an initiative supporting the development of image-guided minimally invasive treatment for prostate cancer. The goal is to develop techniques to define accurately the anatomic extent of localized prostate cancer and to concentrate tumoricidal modalities (interstitial radiation, heat, cold) within the involved area in a manner that spares surrounding normal tissue, preserves function, maximizes quality of life, and reduces the cost of care.
- NCI funded (in total or in part) 246 clinical trials in prostate cancer, including 80 Phase III studies and 37 Phase II studies. NCI clinical studies in prostate cancer have significant African-American participation. One NCI study shows that 14.7 percent of men enrolled onto NCI sponsored prostate cancer treatment trials are African American while 10.3 percent of Americans diagnosed with prostate cancer are African American.
- Clinical Trials Restructuring. NCI and many of the clinical researchers it supports are re-engineering the institute's clinical trials program. The aim is to enrich the scientific input into clinical trials conception and design, streamline operations, and broaden access to trials participation among both patients and physicians across the country. Pilot studies are planned that will test new systems for realizing these goals. Lung and genitourinary cancers will be a special focus of these new planning and expanded access efforts. During the next year NCI expects to begin a series of national State of the Science meetings to define the key areas for

emphasis in prostate clinical research. In a parallel effort, we shall also begin coordinating development of a common methodology for the conduct and analysis of prostate cancer trials, including common endpoints.

- NCI's ongoing Prostate Cancer Prevention Trial (PCPT) involves 18,000 healthy men over the age of 55 to determine if the drug finasteride can prevent prostate cancer.
- NCI's ongoing Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) is assessing the efficacy of prostate cancer screening. New PLCO sites are being added to enhance minority patient accrual. NCI also is co-sponsoring with the Veterans Administrations a trial to determine whether there is a cohort of patients for whom conservative treatment of localized disease may be an acceptable alternative to surgery.
- NCI staff analyzing the Surveillance and End Results (SEER) Program data have shown that there are tremendously differing patterns of care among black and white men with prostate cancer. Encouragingly, however, NCI staff and the Department of Defense have collaborated in a study of treatment data and shown that equal treatment yields equal outcome within disease stages. This finding suggests that NCI efforts to improve prevention, diagnosis, and treatment of this disease have the potential to benefit all patients equally.
- NCI, along with the American Cancer Society and the Centers for Disease Control and Prevention sponsored a Leadership Conference on Prostate Cancer in the African-American Community in November of 1997. Developed in cooperation with the 100 Black Men of America, the Intercultural Cancer Council, the National Black Leadership on Cancer, and the National Prostate Cancer Coalition, the conference represented a significant step toward developing a strategy for the full participation of African Americans in prostate cancer research and control.
- In addition, NCI recently conducted a large interview-based study of prostate cancer in African Americans and whites. Analysis of the results has not thus far revealed any specific factor that could explain the racial differences in risk. However, further studies are underway, including an extensive evaluation of the role of different components of the diet.
- Health Services & Economics Research in Prostate Cancer. The NCI supports studies within its Cancer Surveillance Research Program on the outcomes of prostate-cancer treatment, including assessments of the quality of life. It also is beginning studies to describe patterns of PSA usage after diagnosis and others to construct models that help explain trends in incidence and mortality as a function of screening. Studies of economic aspects of prostate cancer diagnosis and care are also supported, including the cost-effectiveness of cancer control interventions and a grant that employs a database that links Medicare and SEER data to investigate the patterns of care and economics of cancer screening and treatment for prostate as well as lung and colon cancers.

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate. For prostate cancer, the institute communicates information to all of those groups, as well as to the cancer research community. Materials available from NCI, including print, video, and web products, range from basic information about the disease, information about research now ongoing to improve understanding and management of the disease, and information for men about early detection and treatment options.

One of the most recent communications initiatives is a partnership with the prostate cancer advocacy organization, US TOO, to develop a national communications initiative, called *Know Your Options*, to better inform men and their families about the disease. The initiative is based on an information package or kit that provides a solid base of information about prostate cancer to help US TOO chapters work with their hometown media. The media, in turn, use the information provided by US TOO with the NCI endorsement to keep their readers, listeners, and viewers informed about the disease. The kit includes the latest medical and scientific information available, as well as information about where US TOO chapter leaders can go for more information, advice, and help.

In addition, information specialists from the NCI-sponsored Cancer Information Service provide more than 60,000 people annually with information about prostate cancer, information about research on the disease, information about screening and treatment options, and information about coping with physical and psychological side effects of the disease and its treatment. The NCI web site provides information about prostate cancer clinical trials as well as information about treatment options for every stage of the disease.

NCI is currently working with the Centers for Disease Control and Prevention and with the Health Care Financing Administration to develop an educational video for men on issues they could face about prostate cancer screening, diagnosis, and treatment. The video, intended to be relevant to a general male audience, will be developed to have special relevance to African-American men. The video will provide educational material on what men need to know about prostate cancer screening options, what they need to know about diagnostic follow-up if a screening test is positive, and what they need to know about treatment options if the diagnosis is positive.

NCI's basic print product about the disease, *What You Need to Know about Prostate Cancer*, is now available on the web as well. It provides information about prostate cancer; its symptoms, diagnosis, staging and treatment; clinical trials; side effects of treatment; nutrition and other support for prostate cancer patients; and what prostate cancer research holds for the future.

A new publication from NCI, *Understanding Prostate Changes: A Health Guide for All Men*, will soon be available on the web too. It covers all aspects of prostate cancer in more depth than the basic booklet, but also describes non-cancerous prostate conditions. Another product in development, *called Prostate Cancer Treatment: Know Your Options*, will be published in print format soon and will also be available on the NCI web site.

NCI is communicating vigorously with the cancer research community. Earlier this year, NCI staff described all of the prostate cancer research initiatives that exist at the institute, and placed that information on its web site. The institute then promoted the availability of that information and issued an invitation for grant applications from the scientific community. The promotion of the information on the web site including the placement of advertisements in major scientific journals, the distribution of packets of information to the nation's cancer centers, and the distribution of information through direct mail to cancer investigators. Since the promotion began in late February 1999, the web page listing prostate cancer grant opportunities has had thousands of hits from those seeking information about the grant opportunities.

Item

Tobacco -- Tobacco remains one of the leading risk factors in developing cancer. The Committee is pleased that NCI is continuing to support research aimed at preventing and controlling tobacco use and urges the Institute to continue these efforts. (p. 70)

Action taken or to be taken

Current Activities and Future Plans

ASSIST Ends, National Tobacco Control Program Begins

As NCI's ASSIST demonstration project came to an end, the Department recognized the importance of state tobacco control programs and made a commitment to their continuation, as expressed in the President's budget request for fiscal year 1999. This request, which was approved by the Congress, included a major budget increase for the CDC in order to support tobacco control programs like ASSIST in all 50 states. The CDC has implemented a national program, with extensive input from the NCI staff, tobacco control scientists, and health department staff from ASSIST states. The NCI is pleased that this transition of community tobacco control from smaller research projects, to a large demonstration project (ASSIST), and now to a nation-wide program in every state will ensure that the effective community intervention methods learned in ASSIST will be applied to all communities in all 50 states. This transition will serve as a model for other public health arenas of the successful implementation and dissemination of research results. As a result of collaboration between the NCI and the CDC, the National Tobacco Control Program was initiated on October 1, 1999 in all 50 states, territories, and the District of Columbia.

Tobacco Research as an "Extraordinary Opportunity"

For decades, the NCI has made tobacco research a top priority. The NCI has supported a broad spectrum of tobacco related research in the biological, behavioral, and social sciences, and is leading a major trans-NIH program to increase research in the prevention and cessation of tobacco use by youth. The development of a new generation of nation-wide tobacco prevention and control programs is an example of extremely successful collaboration across agencies. The NCI is committed to continuing its strong participation in the field of tobacco research by strengthening its program of basic and behavioral research initiatives in tobacco control research. A constellation of recent scientific, public policy, social, and legal developments has presented the scientific community with an unprecedented opportunity to expand research to reduce significantly the burden of death and disease caused by tobacco use. Consequently, NCI has identified "Research on Tobacco and Tobacco-Related Cancers" as one of its three new "extraordinary opportunities for investment" in NCI's budget proposal for fiscal year 2001. This extraordinary opportunity is different from other important research areas supported by the NCI. It is intended to focus efforts and increase resources which could produce dramatic progress toward reducing the burden of cancer. It will result in new grant or contract awards; collaborative efforts with other Institutes, government agencies, or private sector entities; and

new or expanded scientific programs within the NCI , bringing the NCI to a new era in cancer prevention and care.

The NCI's proposed expanded scope of tobacco research will include development of improved tobacco-use treatment strategies, conduct of genetic epidemiology research, prevention of cancer in former smokers, conduct of basic biological research, expanded surveillance initiatives, and opportunities for the enhancement of the national research infrastructure by increasing the number of transdisciplinary tobacco use research centers, funding of transdisciplinary research and training programs, and the creation of an NCI clinical research program on nicotine addiction and tobacco use.

Youth Prevention and Cessation Research

NCI's emphasis on research initiatives in the area of tobacco use and cessation among the adolescent population has resulted in considerable success in reducing adolescent tobacco use in the late 1970s and early 1980s. The use of tobacco among high school seniors, for whom data with the longest time trends are available, have remained essentially stable for more than a decade, with just under 20% of seniors reporting daily smoking. However, high school dropouts smoke at an alarmingly high rate. One study in Minnesota found that 77% of both male and female 16-year old dropouts smoked on a daily basis; a similar study in Ontario, Canada, found a nearly 68% smoking rate among high school dropouts. When the high school senior tobacco use prevalence rates are considered in tandem with the dropout smoking rates, the smoking prevalence rate among U.S. adolescents nearly equals that among adults, i.e., about 25%. Smokeless tobacco use - spit tobacco - among youth, especially among males, also continues to rise. If these trends continue, the prospect for further reductions in national tobacco use prevalence rates, and accompanying tobacco-related disease rates and economic costs, is unlikely to change substantially in the foreseeable future.

The NCI, in collaboration with the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the National Institute of Dental Research (NIDR), the National Institute of Mental Health (NIMH), and the National Institute of Nursing Research (NINR) published a Request for Applications (RFA) for innovative research that have clear implications for the immediate and significant reduction of tobacco use by children and youth in the United States. As a result of two RFAs, 29 research grants were awarded in 1998 and 1999 in the area of youth and tobacco research. These research projects include prevention, experimentation and onset of regular tobacco use, dependence and withdrawal, and cessation and treatment of tobacco by adolescents.

Tobacco Research Implementation Plan

In 1998, The Tobacco Research Implementation Group (TRIG) was created to establish the NCI's tobacco-related cancer research priorities for the next five to seven years. These priorities are described in the TRIG report entitled, *The National Cancer Institute Tobacco Research Implementation Plan, Priorities for Tobacco Research Beyond the Year 2000*. The group identified nine overarching opportunities for tobacco-related cancer research, emphasizing collaboration with partners in the public and private sectors, such as the National Institute on

Drug Abuse (NIDA), the Centers for Disease Control and Prevention, the American Cancer Society, and the Robert Wood Johnson Foundation. TRIG members were united in their conviction that the NCI should increase its efforts to develop a comprehensive, but focused program of research on tobacco use that will help to reverse the existing epidemic of tobacco-related cancer. The nine research priorities identified by the TRIG are: building the tobacco research infrastructure, basic biobehavioral research, prevention of nicotine use and nicotine addiction, treatment of nicotine addiction, community and state intervention research, policy research, basic biological research, epidemiologic research, and surveillance research. Several new initiatives have already underway, including Transdisciplinary Tobacco Use Research Centers, Research in State and Community Tobacco Control Interventions, Basic Biobehavioral Research, and Review and Analysis of Tobacco Industry Documents. In addition, the TRIG report provided much of the foundation for developing NCI's extraordinary opportunity for investment in tobacco-related research.

Transdisciplinary Tobacco Use Research Centers

In 1998, the NCI and the NIDA issued an RFA inviting grant applications for the creation of transdisciplinary tobacco use research centers (TTURCs) in order to facilitate a transdisciplinary research approach to the full spectrum of basic and applied research on tobacco use. Increasingly, tobacco control and addiction research must rely upon collaboration between scientists with expertise in different fields. Seven transdisciplinary centers were funded September 30, 1999 for five years by NCI and NIDA. Each center is organized around a special theme, such as culture, genetics, animal models of behavior and innovative treatments. Investigators will study prevention of tobacco use, initiation of tobacco use, and addiction. These TTURCs are the first group of major research centers that will focus only on tobacco use, bringing together scientists from a wide range of disciplines. Equally important, these centers will help train the next generation of tobacco use researchers.

Research in State and Community Tobacco Control Interventions

America's communities are the final proving grounds where tobacco control interventions are tested to determine how they work in the real world. Every state will now have a comprehensive tobacco control program, and many states are considering major expansions of these programs. These new and expanded programs raise new research questions and provide opportunities to improve the effectiveness of tobacco interventions. Under this new initiative, developed in 1999, researchers will examine the impact of a variety of tobacco control interventions, including mass media campaigns, public health policies that influence behavior, and other approaches to reducing tobacco use at the state and community levels.

Basic Biobehavioral Research on Cancer-Related Behaviors

This initiative is designed to support innovative ideas focused on links between biology, behavior, and environment as they pertain to cancer-related risk behaviors, such as tobacco use. NCI issued an RFA in 1998 and re-issued it in 1999 in order to stimulate research in this important area. While such research does not address behavior or disease outcomes directly, it enhances knowledge or fundamental mechanisms and the determinants of cancer-related

behaviors. This knowledge is necessary to develop more effective cancer control interventions and to target such interventions to persons most likely to benefit.

Review and Analysis of Tobacco Industry Documents

On July 17, 1998, the President issued an Executive Memorandum highlighting the importance of the tobacco industry documents that have been released as a result of recent tobacco litigation and congressional subpoenas. This initiative, developed in 1999, is one component of the Department's response to the President's directive. It is intended to stimulate research on a wide variety of scientific, technical, marketing, and tactical undertakings by the tobacco industry, which were documented in papers, memos, and other records. The systematic, comprehensive analysis and evaluation of these documents will greatly contribute to the understanding of what the tobacco industry knew and will help researchers and the public health community identify effective strategies to reduce tobacco use.

The other high-priority areas of tobacco research identified by the TRIG will be pursued by the NCI as part of its "extraordinary opportunity for investment" in tobacco-related research. Included in this list are studies of tobacco-related carcinogenesis, basic bio-behavioral research, epidemiology, and surveillance research. For example, NCI has recently funded epidemiological research projects on the effect of smoking cessation on plasma micronutrients, on the effect of vitamin C supplementation on tobacco-related DNA damage, and on tobacco metabolism genes and their role in stomach cancer risk. The NCI is planning an expansion of research opportunities to tailor interventions to specific sociocultural, psychological, physiological and genetic subgroups, research to understand genetic and environmental interactions in susceptibility to tobacco-related cancer, and basic biological research to identify and validate bio-markers of tobacco exposure and tobacco-related cellular events as they relate to cancer. The NCI is committed to an expanded research program to inform all efforts to reduce tobacco use, in schools, health care settings, and throughout our communities. The NCI's commitment to research, in combination with our proven ability to collaborate with a large number of research and public health organizations, has the potential to have a significant impact on the way tobacco research is conducted on a national scale, and will speed the pace of discovery and public health benefit by reducing tobacco use and the incidence of tobacco-related cancers.

Item

Urological Cancers -- The Committee commends the new initiatives proposed for prostate cancer and urges the Institute to develop a plan to expand its research for other urologic cancers, such as kidney and bladder cancer, to take advantage of new knowledge that has been acquired about cancer diagnosis and treatment. (p. 70)

Action Taken or to be taken

The magnitude and trends in urological cancer are being tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Cancers directly related to the urinary system (urinary bladder, kidney/renal pelvis, and ureter/other urinary organs) total over 86,000 new cases each year and nearly 25,000 deaths. Cancers of the urinary bladder alone were diagnosed

over 54,000 times in 1999 and accounted for the deaths of over 12,000 Americans. In the SEER regions, for the period 1988 to 1992, the incidence rates are generally three to four times higher in men than in women. Among men, the highest rates are in white non-Hispanics (about 33 per 100,000). The rates for black men and Hispanic men are similar and are about one- half the white, non-Hispanic rate. The lowest rates are in the Asian populations. For women, the highest rates are also in white non-Hispanics and are about twice the rate for Hispanics. Black women, however, have higher rates than Hispanic women. The incidence of bladder cancer increases dramatically with age among men and women in all populations. Rates in those aged 70 years and older are approximately two to three times higher than those aged 55-69 years, and about 15 to 20 times higher than those aged 30-54 years.

Mortality rates are two to three times higher for men than women. While incidence rates in the white population exceed those for the black population, such is not the case for mortality where the rates are much closer together. Black women who have a lower incidence of bladder cancer than white women actually die from the disease at a greater rate. This difference in survival between black and white populations reflects the fact that in whites a larger proportion of these cancers are diagnosed at an early more treatable stage. Mortality rates for Hispanic and Asian men and women are only about one-half those for whites and blacks.

Through research sponsored by the NCI, cigarette smoking has been established as a risk factor for urinary bladder cancer. It is estimated that about 50% of these cancers in men and 30% in women are due to smoking. Occupational exposures may also account for up to 25% of all urinary bladder cancers. Most of the occupationally accrued risk is due to exposure to a group of chemicals known as arylamines. Occupations with high exposure to arylamines include dye workers, rubber workers, leather workers, truck drivers, painters, and aluminum workers. Because of this association with bladder cancer, some arylamines have been eliminated or greatly reduced in occupational settings. Coffee, alcohol, and artificial sweeteners have all been studied as risk factors for bladder cancer, but associations, if they exist, are weak. The greatest prevention strategy is reduction in the consumption of cigarettes. We now know that cigarette use increases one's risk for bladder cancer by two to five times, but when cigarette smokers quit, their risk declines in two to four years.

Most bladder cancers are carcinomas of the transitional epithelium of the bladder's mucosal lining. Although 90% of the cases are localized at diagnosis, up to 80% recur. Tumors are graded according to the degree of cellular abnormality, with the most atypical cells designated as high-grade tumors. Staging of this cancer is based on the depth of invasion into the bladder muscle and surrounding structures. In the United States, approximately 95% of malignant bladder lesions are transitional cell carcinomas. Of the remaining neoplasms, 3% are squamous cell carcinomas, and the remainder are adenocarcinomas. One of the problems in managing the disease is that the carcinoma of the bladder frequently multifocal. The entire bladder epithelium and the lining of the entire urothelial cell tract can undergo malignant change. After apparently successful treatment of a bladder lesion, new tumors may occur at the same site (recurrence) or other urothelial cells in the bladder. Approximately 30% of bladder carcinomas appear as multiple lesions at the time of initial diagnosis.

The NCI has an extensive research portfolio related to bladder cancer with over 80 individual research projects funded. The aims of these projects range from understanding the genetic and environmental risk factors for bladder cancer to better and earlier detection of bladder cancer to preclinical studies aimed at understanding the molecular basis of the disease to clinical trials. A variety of clinical trials related to bladder cancer are ongoing. The NCI's PDQ database lists 177 such trials of which 117 are NCI-sponsored. Of these, 89 are Phase I trials in which novel treatment approaches are being assessed for safety and nine are Phase III trials wherein new treatment approaches are closest to being introduced into general medical practice. New ways of using traditional chemotherapeutic agents are under study as are treatment with cytokines and gene therapy.

The second most common cancer related directly to the urinary system is kidney cancer. Cancers of the kidney and renal pelvis are diagnosed in the U.S. approximately 30,000 each year, and nearly 12,000 Americans die each year of these cancers. In kidney cancer too, the NCI is supporting a broad range of research projects with approximately 90 such projects currently funded by the NCI. Intramural researchers are studying the molecular genetics of familial kidney cancer, and through these efforts significant new insights have been gained not only into the genetic basis of the rarer inherited form of kidney cancer but also into the more common sporadic (non-inherited) form of the disease. The NCI's PDQ database contains 114 clinical trials related to kidney cancer of which 114 are NCI-sponsored. Of these clinical trials, 84 are Phase I trials and 3 are Phase III trials.

The NCI Director and other NCI staff meet regularly with members of the American Urological Association to foster increased cooperation between the NCI, this professional organization, and the urological physician community that it represents. The NCI established the Urologic Oncology Branch to expand and encourage clinical and basic research conducted in all aspects of urological cancers. The Urologic Oncology Branch offers investigative and experimental treatments for patients with a variety of cancers, including kidney, prostate and bladder cancer. All patients in the Urologic Oncology Branch are treated on the urology clinical unit on a research protocol. Medical treatments and transportation are free of charge once patients are accepted on a research protocol. Patient evaluation and care takes place at the NIH Clinical Center which is a full service 350 bed hospital located on the NIH campus and devoted to NIH-sponsored clinical research. The Branch coordinates the trans-NIH Prostate Cancer Interest Group, which is committed to expansion of both basic and clinical research on prostate cancer. The Urologic Oncology Branch also coordinates the NIH Kidney Cancer Working Group made up of over 60 individuals from 8 different Institutes/Centers. The NCI has recently established a similar Bladder Cancer Working Group.

Investigators in the Urologic Oncology Branch are involved in the conduct of laboratory and clinical research aimed at improving the treatment of patients with urologic cancers. In addition, the Urologic Oncology Branch has a major commitment of providing urology surgical consultative care for patients throughout the Clinical Center. Laboratory research emphasizes studies of cancer genes and molecular genetic aspects of hereditary as well as sporadic forms of kidney, prostate and bladder cancer. These studies include research into the clinical and basic aspects of kidney cancer (especially Von Hippel-Lindau disease, hereditary renal oncocytoma, and hereditary papillary renal carcinoma), prostate cancer and bladder cancer. Clinical efforts

emphasize the development of new approaches to treatment and diagnosis of urologic cancers as well as the development of innovative surgical approaches to the treatment of patients with primary or metastatic urologic cancers.

Von Hippel-Lindau (VHL) disease is an inherited disorder that affects one in 32,000 people worldwide. Adults with VHL have frequent recurrent tumors, primarily in the kidneys, retinas, and the central nervous system. VHL disease is caused by mutations in the VHL gene, first identified by NCI-supported researchers. Since its discovery, it has been learned that the VHL gene is susceptible to mutations at many different points, resulting in different types of tumors. It has also been established that the VHL gene is involved in non-inherited kidney cancers as well as in VHL disease. The discovery and characterization of the VHL gene has allowed for genetic testing of first-degree relatives of affected individuals, which provides an early warning system for individuals harboring a mutated VHL gene. Improved imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) scans are also enabling earlier detection and better management such as kidney-sparing surgery for VHL patients.

In 1992, the NCI established the Specialized Programs of Research Excellence (SPOREs) to promote interdisciplinary research and to speed the bidirectional exchange between basic and clinical science to move basic research finding from the laboratory to applied settings involving patients and populations. The goal of the SPORE program is to bring to clinical care settings novel ideas that have the potential to reduce cancer incidence an mortality, improve survival, and to improve the quality of life. Laboratory and clinical scientists work collaboratively to plan, design and implement research programs that impact on cancer prevention, detection, diagnosis, treatment and control. To facilitate this research, each SPORE develops and maintains specialized resources that benefit all scientist working on the specific cancer cite, as well as SPORE scientists. An additional SPORE element is a career development program that recruits scientists both within and outside the SPORE institution to enlarge the cadre of laboratory and clinical scientists dedicated to translational research on human cancer. SPOREs meet annually to share data, assess research progress, identify new research opportunities and establish priorities for research most likely to reduce incidence and mortality and to increase survival. In 1998, NCI funded a total of 14 SPOREs and co-funded six SPOREs for a total of $30 million. SPOREs are funded through specialized center grants (P50s).

In the upcoming years, NCI will increase the use of the SPORE mechanism to include funding for other major cancer sites. In September 1999, a Program Announcement was issued by the NCI for additional SPOREs to conduct the highest quality balanced translational research on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer. SPOREs are at institutions that will make a strong commitment to the organization and conduct of these programs. SPORE applicants are judged on their current and potential ability to translate basic research findings into innovative research settings involving patients and populations. A SPORE is also encouraged to conduct research on rehabilitation and quality-of-life. A SPORE must develop and maintain human cancer tissue resources for the particular organ-site that will benefit translational research; develop extended collaborations in critical areas of research need with laboratory scientists and clinical scientists within the institution and in other institutions; and participate with other SPOREs on a regular basis to share positive and negative information, assess scientific progress in the field, identify new research opportunities,

and promote inter-SPORE collaborations to resolve areas of scientific controversy. Each SPORE and the networks of SPOREs are expected to conduct research that will have the most immediate impact possible on reducing incidence and mortality of human cancer. A SPORE should support a mix of basic and clinical researchers whose formal interactive and collaborative research efforts will result in new approaches for early detection, diagnosis, therapy, and prevention and control. The SPORE mechanism is not intended to support basic research to the exclusion of clinical research or vice versa. A SPORE conducts translational research that requires interdependence between basic and clinical investigators in both the planning and implementation of research and emphasizes the application of basic research findings to patients and populations.

Based on NCI's projections regarding the growth of the SPORE program, it is anticipated that applications for a SPORE focused on prostate and genitourinary cancers will occur in fiscal year 2000, fiscal year 2002, fiscal year 2004 and fiscal year 2005.

Fiscal Year 2000 Senate Appropriations Committee Report Language (S. Rpt.106-166)

Item

[Imaging technology] -- The Committee is encouraged by the recent conference held by NCI on biomedical imaging and urges NCI to take a leadership role with the Food and Drug Administration and the Health Care Financing Administration to avoid duplicative reviews of new imaging technologies which may prevent their benefits from reaching patients on a timely basis. The Committee is aware of the great potential for improved patient care and disease management represented by molecular imaging technologies, especially positron emission tomography (PET) through its ability to image the biology of many kinds of cancer and other diseases. The Committee supports NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee encourages the large scale testing of women for breast cancer and of men for prostate cancer to demonstrate and quantify the increased diagnosis and staging capabilities of PET relative to conventional diagnostic and staging technologies including mammography.

The Committee is aware of the striking advances in high-resolution imaging technologies of functional magnetic resonance imaging and spectroscopy, and optical coherence tomography for detecting small abnormalities in tissues and for solving the structure of important cellular molecules. Given the recent data showing a high rate of false-positive diagnoses of breast cancer from current mammographic technologies, the Committee believes there is a critical need to bring these important new technologies to full development for the diagnosis of breast cancer at earlier stages than currently exists. Therefore, the Committee urges favorable consideration for funding accelerated development and implementation of these advanced imaging systems and processing technologies. (p. 111)

Action taken or to be taken

As recently as 25 years ago, a physician or surgeon who suspected the presence of a tumor in a patient had few options: order x-ray studies to define and localize the tumor as accurately as the

pictures would permit, schedule the patient for surgery and examine the tumor directly, excise a portion of the unhealthy tissue for biopsy, remove the tumor if possible, and explore surrounding tissues to determine whether the cancer had spread.

Over the last quarter century, refinements in imaging technology have substantially broadened the range of medical options. Current imaging tests now provide much clearer and more detailed pictures of organs and tissues than were possible previously. Imaging already has had a lifesaving effect in detecting some early cancers. X-ray mammography, for example, has saved the lives of many women by revealing the presence of very small cancers before they could be detected by physical examination. Computed tomography (CT) and ultrasound permit physicians to guide long, thin needles deep within the body to biopsy organs, often eliminating the need for an open surgical procedure. CT can reveal whether a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs; important information that can help guide treatment choices.

Digital Mammography

Four manufacturers have produced prototype test digital mammography units. Limited clinical trials are underway for the purpose of securing FDA permission to market the devices. The FDA has withdrawn its original (1996) Guidance, "Information for Manufacturers Seeking Marketing Clearance of Digital Mammography Systems," and has not completed a new Guidance, so the approval path for digital mammography devices is not clear.

NCI believes that it is important to support research aimed at optimizing digital mammography technology and to support clinical trials. Data from the clinical trials currently underway will help determine whether and what kind of large-scale clinical trials may be necessary. The goal is to determine whether digital mammography is better than conventional film-screen mammography, and if it is, of what kind and how large the improvements are.

To promote the optimization of the digital mammography system, the NCI has issued a Program Announcement inviting applications for Development and Testing of Digital Mammography Displays and Workstations. Eleven applications were received in the first cycle. Applicants proposed the improvement of monitors, the creation of workstations and their testing in the clinical setting. The first awards under this Program Announcement will be made after the NCAB meeting.

Regarding the need for large-scale testing of women to quantify the increased detection success of digital mammography relative to film/screen mammography, NCI staff members have discussed possible trial design internally and developed recommendations. This group has also reviewed the current protocols of digital mammography trials funded by industry or government agencies, observing their progress in patient accrual. The NCI-funded American College of Radiology Imaging Network (ACRIN) was asked to develop a protocol and accompanying budget to carry out a large-scale trial. The first draft of the protocol has been completed and submitted to NCI for review, discussion, and feasibility determination. By spring, 2000, the NCI will discuss with its over-site and advisory boards how this trial fits into its overall priorities and funding plans.

Application of Imaging Technologies to Breast Cancer

Important advances in imaging systems are being applied to the detection of breast cancer. The NCI is funding research on a variety of technologies for breast imaging. These techniques for breast imaging include:

- Elastography
- Magnetic Resonance Imaging (MRI)
- Magnetic Resonance Spectroscopy (MRS)
- A Number of Ultrasound Techniques
- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT) using a number of compounds designed to look at molecular biological and metabolic characteristics
- Optical Technologies emphasizing the use of the near-infrared region of the spectrum.

A multi-center, international clinical trial on the use of MRI in the detection of breast cancer is being funded. Nearly four hundred patients have been accrued at 10 centers in this trial to test MRI as a tool to decrease the number of false-positive X-ray mammograms that lead to biopsy. NCI is also funding a multi-center trial of breast MRI as a screening test for breast cancer in women at high risk for breast cancer. The NCI initiated funding in fiscal year 1999 a large, 5-year project combining the development of four of the above technologies, which will all be tested in a group of interested women arriving for mammography. Ongoing research in digital mammography, in 11 projects, includes x-ray source and digital detector development, image optimization and interpretation studies, and studies of impact and cost.

Imaging Systems Technologies

Status of Ongoing Programs - Program Announcements

Exploratory/Developmental Grants for Diagnostic Cancer Imaging

This Program Announcement, originally issued in 1997, provides support for 2 years of funding at a level adequate for the initial feasibility testing and generation of experimental preliminary data. There exists a need for innovative and creative approaches leading to new avenues of research, and one way to encourage high risk/high impact research is to provide investigators with the initial resources required to accomplish pilot testing of ideas. Since the inception of this ongoing program, 143 applications have been received, and an estimated 39 grants will be funded during fiscal year 1999-2000.

Development of Digital Mammography Displays and Workstations

Digital Mammography is one of the most promising research areas for improving early detection of breast cancer. However, there is a need for a concerted effort to overcome the problems of displaying the digital mammograms, so that they are accurately interpretable for diagnosis. In 1999, the NCI issued this Program Announcement in order encourage research in this area, from

both academic investigators and small businesses. For the February 2000 NCAB, there were 11 investigator initiated applications received.

Innovative Technologies for the Molecular Analysis of Cancer: Phased Innovation and Small Business Awards

Applications of Innovative Technologies for the Molecular Analysis of Cancer: Phased Technology Application and Small Business Awards

This series of four program announcements focuses on the development and application of molecular analysis technologies in studies relevant to cancer research. Molecular analysis technologies of interest include those that are entirely novel, or emerging but not currently in broad scale use, or technologies currently in use for one application or set of applications, that are being evaluated for utility for alternative applications. Imaging research, including chemistries, hardware and computational tools to support imaging of molecular species in cells or whole organisms, can be supported under this program. Currently, one imaging project is funded through this mechanism.

Novel Technologies for Noninvasive Detection, Diagnosis and Treatment of Cancer

The Unconventional Innovations Program (UIP) sought proposals that represented the highest potential for revolutionary breakthroughs in the development of technologies to enable the non-invasive sensing of cancer signatures in the living body coupled to capabilities for monitored intervention. These approaches typically carry substantial risk of failing to meet long term objectives. As a result, the NCI issued this request as a demonstration of its commitment to explore these high risk approaches. The UIP was specifically soliciting projects to develop technology systems or systems components to enable sensing of defined signatures of different cancerous or precancerous cell types or their associated microenvironment in the body in a way that is highly sensitive and specific, yet non-intrusive. The highest priority was for systems that can either support or provide a seamless interface between sensing/detection and intervention. Of the five awards that were made in fiscal year 1999, four of them either use imaging or are developing imaging tools as part of a more complex system.

Bioengineering Research Grants (BRGs) and Bioengineering Research Partnerships (BRPs)

These are joint initiatives from many Institutes and Centers (ICs) of the National Institutes of Health (NIH) to support basic bioengineering research whose outcomes are likely to advance health or health-related research. Bioengineering integrates principles from diverse fields, and the creativity of interdisciplinary teams is resulting in new basic understanding, novel products and innovative technologies. Bioengineering also crosses the boundaries of academia, science, medicine, and industry. These bioengineering projects are often focused on technology development rather than on proving or disproving a scientific hypothesis, and therefore, the NIH review criteria for bioengineering proposals in response to these PAs have been modified to ensure that these proposals are evaluated appropriately and fairly. Applications are encouraged from individual investigators (BRGs) or multidisciplinary groups of investigators (BRPs). Many

applications for both BRGs and BRPs have been submitted by the imaging community, and the status of funding for those applications will be determined in fiscal year 2000.

Status of Special Initiatives - Requests for Applications

Cooperative Trials in Diagnostic Imaging

The American College of Radiology Imaging Network is an NCI-sponsored Cooperative Group that was established in December 1998, to perform multi-institutional clinical trials in diagnostic imaging related to cancer in a timely and flexible manner. As a national clinical trials resource, ACRIN provides a stable infrastructure within which to conduct clinical trials. If investigators have an idea for a large-scale clinical trial, but do not have access to sufficient numbers of clinical patients to adequately implement such a trial, ACRIN resources are competitively available. ACRIN has a number of clinical trials in various stages of readiness. The first study will compare clinical Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging to pretreatment evaluation by CT and MRI in cervical cancer. Other studies will include an investigation into the use of PET imaging of lung cancer to determine response to chemotherapy, a randomized clinical trial to determine the usefulness of low-dose, spiral CT imaging for detecting early stage lung cancer, and a comparative analysis of display systems for CT colonography, which is also referred to as virtual colonoscopy.

Development and Application of Imaging in Therapeutic Studies

This initiative, issued for funding in fiscal year 1999, was designed to support research projects addressing the development and application of labeled therapeutic agents as compounds for imaging studies, and/or the development and application of imaging agents as metabolic markers of response to newly-developed therapeutic agents. In response to this RFA, 33 applications were received. Four awards were funded in fiscal year 1999 and five more awards are anticipated for fiscal year 2000. The funded research focuses on a wide range of cancer therapies using numerous different imaging methodologies, including PET, SPECT, MRI and MRS. PET technologies are of particular importance in these studies. One project will use PET imaging to monitor and facilitate the evaluation of gene therapy in pilot patient studies. Another project will incorporate PET radiotracers into a multi-modality imaging agent capable of tracking the effect of drug activation in cancer cells. Other applications will use PET imaging agents to interrogate the response of cancer to therapies that disrupt cellular metabolic pathways that are difficult to monitor non-invasively.

Small Animal Imaging Resource Programs (SAIRPs)

Small animal models, particularly genetically engineered mice, are increasingly recognized as powerful discovery tools in cancer research. Functional, quantitative imaging techniques are an important tool for providing data about biochemical, genetic or pharmacological processes in vivo, and repetitively in the same animal, without having to sacrifice the animal for analysis. This program, issued in fiscal year 1999 will provide both shared imaging research resources to be used by cancer investigators and research related to small animal imaging technology.

Twenty nine applications were received in November 1998 in response to this announcement, and five grants have been funded.

In Vivo Cellular And Molecular Imaging Centers (ICMICs) and (Pre-ICMICs)

In Vivo Cellular And Molecular Imaging Centers are designed to capitalize on the extraordinary opportunity for studying cancer non-invasively, and in many cases, quantitatively due to recent advances in molecular imaging modalities, and molecular and cellular biology. The ICMICs and Pre-ICMICs will facilitate the interaction of scientists from a variety of fields to conduct multidisciplinary research on imaging at the cellular and molecular level. Two types of grants will be awarded, the Planning Grant (RFA CA-99-002) and the Specialized Center Grant (RFA CA-99-004). Pre-ICMICs will provide funding for groups to formally plan and establish the organizational and operational structure necessary for new, multidisciplinary collaborative scientific efforts. The five-year ICMIC grants will be appropriate for those institutions that are already supporting investigator-initiated multidisciplinary research involving imaging and molecular technologies but which lack the overall structure and resources necessary to take full advantage of emerging opportunities. The Specialized Center grant will provide a formal framework through which scientific synergy can occur on a stable and continuing basis.

The funding for the ICMICs and Pre-ICMICS is planned to start in fiscal year 2000, and the first deadline for receipt of applications was in July 1999. Response to this initiative has been very good: 27 applications for Pre-ICMIC grants were received (with an estimated six grants to be awarded), and five applications for ICMICs were received (with an estimated two grants to be awarded).

Diagnostic Imaging and Guided Therapy in Prostate Cancer Grants and Small Business Grants

This initiative, issued in August 1999, is designed to encourage research on improved imaging methods for the localization, biopsy and image-guided biopsy or therapy of prostate cancer. The specific goals include the development and application of one or more of the following inter-related components: (a) means for measuring local extent of disease using anatomic, metabolic or alternative novel imaging methods, (b) means for improved image-guided biopsy, staging or identification of aggressive cancers by metabolic or alternative novel imaging methods, and (c) means for navigation and control of image-guided therapy or measurement of early biological effects of therapy. Although the deadline for applications is in November 1999, letters of intent (LOI) to submit an application have been received, and the response has been very enthusiastic. Approximately 50 LOIs were received for phased innovation applications, with an estimated six to eight applications to be funded. Approximately 20 LOIs were received from small businesses.

New Initiatives Planned for Fiscal Year 2001

Image Database Resource for Image Processing Research

Biomedical imaging is increasingly electronic in terms of image acquisition and display. The conversion of that electronic information into an image requires sophisticated computer software and hardware. However, the development of optimized, and generalizable, computational

methods has been hampered by the lack of standardized sets of data upon which to test new algorithms and display the results. This proposed RFA will support a consortium of institutions to develop the necessary consensus and standards for a lung CT image database resource, and to construct a database of spiral CT lung images. This initiative will essentially serve as a demonstration project, to demonstrate that a group of experts focussing on just one organ system and one modality may develop a process that will serve as a model for other groups to develop additional image database resources.

Development of Novel Imaging Technologies

This proposed Program Announcement is directed at the development of imaging methods and enhancers, and limited evaluation or feasibility studies using either pre-clinical or clinical models. The intent is to stimulate: (a) the development of highly innovative imaging methods and enhancement methods, including high risk/ high gain technologies that exploit our expanding knowledge of the molecular basis of cancer, and (b) the integration of these emerging and more traditional technologies for more effective solutions for cancer.

Ultrasound Research Interface

Clinical ultrasound procedures currently comprise a significant fraction of imaging studies in the United States. For example, Medicare reimbursements alone are more than twice that of all magnetic resonance (MR) procedures. Thus, ultrasound is a leading modality in terms of its clinical impact. The exponential expansion of MRI in the 1980s and early 1990s occurred because manufacturers provided research interfaces for use by imaging researchers. Clinical and basic research efforts in the academic sector greatly strengthened the commercialization and wider application of MRI systems for cancer research and other disease processes. An ultrasound interface is necessary as a research resource to accomplish the same goals for sonography.

In ultrasound medical imaging, radio frequency (RF) pulses stimulate a transducer probe to generate ultrasound waves. The detected echoes reflected from different biologic structures form images. However, access to raw unprocessed echo data is not possible in commercially available ultrasound machines as it is in MR or CT. This is a barrier to research on new ultrasound techniques. Manufacturers' reluctance in providing access to the echo data has been based on cost, proprietary issues, safety, and liability considerations. Cost factors did not pose major problems for MRI or CT research interfaces, as the interface cost was a small fraction of the total imaging system cost. However, the cost of an ultrasound research interface is large compared to the unit cost of an ultrasound system. Ultrasound manufacturers have agreed that proprietary, safety, and liability issues can all be addressed, but there is a need for government financial support to develop the research interfaces. An investment in the development of such interfaces would produce enormous gains in research productivity and the development of new ultrasound imaging systems.

The intent of this RFP is to develop powerful ultrasound research interfaces that allow extensive control over a wide range of system parameters. These interfaces will be software add-ons to continuously evolving scanner control software. Although the creation of these interfaces

necessarily relies on access to proprietary information, protective software shells can restrict such access while still allowing access to control parameters. This RFP will allow research interfaces to be developed by several leading ultrasound manufacturers to maximize the research impact for the ultrasound imaging community.

The operational characteristics required by this contract will allow the user to: (a) find targets of interest using conventional (commercially-available) B-mode and Doppler methods, (b) enter into a "research mode" with user-programmed scanner parameters, and (c) store raw echo signals during operation in the research mode. The "raw signals" in this context are defined as digital data, either radio frequency (RF) signals or quadrature signals. Recorded waveforms will be beam-formed echoes resulting from a single transmit focus that has not been subjected to nonlinear processing. All of the echo data displayed in the image will be recorded in a data file. There will be ability to externally trigger digital data acquisition. Standard apodization functions should be applied, e.g., rectangular and Hanning. The user interface should execute commands through a single system prompt. The display should indicate the min and max A/D values to show the user how much of the dynamic range is being used. The time between any request for digital data and the acquisition should be known. It should be kept to a minimum, e.g., less than one second. Although no standardized data file format is specified, there should exist a file header with all the information necessary to fully interpret recorded data. It should be possible to read the file, including header information, with standard technical computing languages.

Safety Requirements: The system display should clearly indicate to the end user that a Research mode is active. This must include a prominent message on the display(s) and an exterior label warning that a non-clinical mode is possible. The system should automatically revert back to normal clinical mode when the patient's name is changed. Information about digitization rates, filtering, external triggering, TGC settings, calibrated output power and overall gain settings, frame-recording time stamp, and all aspects of beam-forming should be provided. These safety factors will assist in research site applications for IRB approval and may help industry to later meet FDA requirements for safety if this interface becomes integrated into their commercial ultrasound systems.

Development of Clinical Imaging Drugs and Enhancers (DCIDE)

DCIDE will be a competitive program to expedite and facilitate the development of promising imaging enhancers (contrast agents) or molecular probes from the laboratory to proof of principle clinical trials. This program is modeled on the NCI-funded RAID program that facilitates development of new therapeutic drugs and biologics. The RAID program will increasingly foster the development of target-based therapeutics. Related imaging agents will be necessary for the resultant target-based clinical trials to non-invasively determine where and how the target-based therapeutics are performing in patients. The DCIDE program is intended to supply or enable missing steps so that promising discoveries can be translated to the research and clinical environments in the absence of development capacity, clinical connections, or industry interest. The DCIDE program will focus on promising imaging agents that are not otherwise likely to receive an adequate and timely evaluation. The DCIDE program is not intended by itself to provide full-scale clinical development but will facilitate the performance of clinical trials to establish proof of principle of a compelling hypothesis. Once this is accomplished for

specific products, it is anticipated that clinical development will continue along established lines under the sponsorship of either private companies or the NCI. Through the DCIDE program, the developer of a promising imaging agent or probe will be given access to the development resources of the NCI to remove the most common barriers between laboratory discoveries and clinical trials. Increasingly, imaging probes may consist of an assembly of biologically active agents, including ligands, linkers and signal-generating moieties. Therefore, while acting as a contrast agent or enhancer from a developmental and regulatory perspective, these agents may require a broad approach for successful development into clinical trials.

Item

[Digital mammography] -- The Committee encourages large-scale testing of women to demonstrate and quantify the increased detection capabilities of digital mammography relative to conventional film processes. Because of the rapid advances being made in the technological development of mammography systems, the Committee is concerned that the newest generation of digital mammography systems be used to implement this large-scale testing. The Committee encourages the National Cancer Institute to be prepared to report to the Committee during the fiscal year 2001 hearing, the feasibility of conducting large-scale testing that includes provisions for the use of the most current digital scanning technologies. (p. 111)

Action taken or to be taken

Please refer to pages NCI - 137 through NCI - 145 of this document for NCI's response to this significant item regarding Digital mammography.

Item

Research affecting women and girls -- The Committee believes that health services research involving and affecting women and girls, particularly minorities, has not received adequate attention. The Committee urges NCI to identify and examine the critical nonfinancial barriers to the utilization of vital preventive health services. In addition, the Committee encourages the Institute to develop and evaluate behavioral interventions for health promotion and disease prevention among minority women and girls. These include, but are not limited to, changing diet and exercise; smoking cessation; and the impact of psychosocial factors on the primary prevention of cardiovascular disease and breast, cervical and ovarian cancers in African-American women. The Institute is also encouraged to evaluate the significant role played by psychosocial interventions in the treatment and recovery from cardiovascular disease and breast, cervical, and ovarian cancers. (p. 111-112)

Action taken or to be taken

The Institute maintains a large portfolio assessing use of preventive services and how to encourage their use. The newly created Applied Sociocultural Branch in the Division of Cancer Control and Populations Sciences promises to expand this portfolio of research. The projects listed below are representative of NCI's research portfolio related to health services research

involving females and the barriers to utilization of health services as well as studies on how to change dietary habits.

Behavioral Study related to the Early Detection of Cancer and Smoking Cessation

“Enhancing Cancer Control in a Community Health Center" was a recently completed project aimed at promoting early detection of breast and cervical cancer and smoking cessation in a community health center which serves a predominantly African-American population. Patient-directed interventions (birthday packets with personalized birthday cards and reports and ethnically appropriate patient education materials and telephone counseling), physician-directed interventions (physician education, reminders and health assessment forms) and system-directed interventions (a computerized prompting and reminder system) are being evaluated. Preliminary assessments already show that there was a significant increase in cessation among African Americans who received the tailored print material.

Studies of Tobacco Use by Women

NCI is currently funding 13 projects that include a specific focus on women’s tobacco use; three of these are targeted specifically at pregnant women. Several studies have been funded to assess effective smoking cessation strategies in women, including cognitive behavioral strategies, exercise, self-help booklets, physician intervention and telephone counseling. A study at Boston University is determining the role of smoking as a factor in cancer, cardiovascular disease and other major illnesses among black women. A project at the University of South Carolina is investigating the possibility of a synergistic relationship between Human Papilloma Virus, diet, smoking and race in the development of cervical cancer. Their study group is low income and rural women, who tend to have a high prevalence of smoking. A study at Columbia University, New York is aimed at identifying whether cigarette smoking is associated with an increased risk of breast cancer in women with variants of the N-acetyltransferase 2 enzyme gene (NAT2).

Most women who smoke want to quit. Many attempt to quit each year. However, relapse to smoking is a very significant problem. NCI has funded a study of the use of hand held computers to deliver relapse prevention messages. The computer allows the delivery of specific, individualized, situation-specific messages to help prevent relapse.

Lastly, it has long been recognized that a link exists between smoking and depression, which is far more common in women than men. Evidence also suggests that many women use cigarettes to cope with dysphoric states - anxiety, anger and depressed mood. NCI has funded a study at the University of Michigan to assess the effects of the nicotine patch versus a placebo on smoking abstinence, and the ability of the antidepressant fluroxetine to ameliorate depression/dysphoria during smoking abstinence.

Behavioral Studies related to Breast Cancer Screening

A study entitled "Increasing Breast Screening Among Nonadherent Women" is comparing the effectiveness of tailored telephone counseling in five regions of the U.S. and assessing the cost-effectiveness of the intervention attempts to increase screening among nonadherent women.

This work is critical to designing efforts to increase compliance of minority elderly women with breast cancer screening guidelines. The Duke Comprehensive Cancer Center and Kaiser Permanente are comparing two tailored interventions for women -- print versus telephone counseling -- compared to usual care. Baseline telephone interviews will be conducted in the first year to assess knowledge, beliefs and practices of nonadherent women. Follow-up interviews will be conducted with the cohort in the last quarter of the fourth year.

The research focuses on the important question of how to motivate nonadherent women to participate in regular breast screening. There should be wide generalizability since the research is being conducted in five settings across the country with a range of comparisons across delivery settings and populations. The interactive collaborators include the Fred Hutchinson Cancer Research Center, State University of New York at Stonybrook, the University of Massachusetts and the University of California at Los Angeles.

Pathways to Screening in Four Ethnic Groups

Pathways to Screening in Four Ethnic Groups was a large, multicenter grant administered by the Northern California Cancer Center, Union City, California. This project developed and evaluated culturally targeted cancer control interventions to increase the use of early cancer detection in five ethnic groups in the Greater San Francisco Bay Area. The program encompassed a multi-disciplinary group of affiliated investigators, and the target populations reflected the ethnic heterogeneity of this region. The research approach began from a common Pathways to Screening Framework in which the successful adoption of early cancer detection is viewed as a continuum starting from basic knowledge and attitudes to the procedural and organizational aspects of the delivery process itself. The projects had leadership from their targeted ethnic groups and focused on aspects of the Pathway that were felt to have the greatest impact on screening behavior based on the investigator's research, experience, and knowledge of the community. The projects were:

- Pathways to Early Cancer Detection for Hispanics
- Pathways to Early Cancer Detection for Vietnamese
- Pathways to Early Cancer Detection for African Americans
- Pathways to Early Cancer Detection for Chinese Americans

Synergistic aspects of the Program Project, in addition to use of a common research framework and theme, included the cross-project functions of three central cores in Administration, Cross-Cultural Studies, and Biostatistics and Data Management, the use of the Survey Research Center of the University of California for all major surveys, a coordinated instrument development process, the use of common core questions to provide a rich database for cross-cultural studies, and common data management and analytic procedures. This research allowed development of culturally appropriate interventions and educational materials will benefit similar ethnic/racial populations in other areas of the United States.

Nutrition Studies to Assess the Relationship between Diet and Cancer

An estimated 35% of all cancer deaths in the United States may be attributable to dietary factors (Doll and Peto, 1981). NCI supports USDA recommendations that all Americans reduce their intake of dietary fat to 30% or less of total calories and increase their intake of fruit and vegetables to five to nine servings per day. Eating fruits and vegetables may reduce the risk of cancer and can improve overall health. Despite evidence for the health benefits of fruit and vegetable consumption, only 23% of adults consumed the recommended five or more daily servings in 1991 (Subar et al., 1995). Consequently, NCI launched the national 5-A-Day For Better Health Program in 1991 to encourage Americans to enhance their consumption of fruits and vegetables every day for better health. According to national food consumption surveys, many minority populations consume less fruits and vegetables than the national average.

The following sections highlight intervention studies designed to change dietary habits in adolescents, and describes in detail the NCI 5-A-Day For Better Health Program.

Reducing Dietary Risk Behavior in Adolescents

A study entitled "Reducing Cancer-related Dietary Risk Behaviors in Adolescents" is being conducted by the University of Minnesota to assess the feasibility of increasing student intake of fruits and vegetables and reducing their intake of calories from total fat. Nutritional surveys indicate that children and adolescents are eating a diet that does not meet recommended intakes of fruits and vegetables and that exceeds recommended intake of energy from total fat. It is believed that these dietary patterns, which are learned in childhood and continue into adulthood, predispose American youth to increased risk of some types of cancer, including breast, colon and stomach cancer. Populations that are of lower socioeconomic status have higher incidence rates of these and other cancers.

This study is implementing a two-year, multi-component school-based program targeting multi-ethnic, lower socioeconomic students, their families, and their school environment. There are a total of 20 schools from two inner-city school districts (Minneapolis and St. Paul) that are being randomized to either the intervention or the delayed-program condition. These schools enroll a disproportionately large number of Minnesota minority children and children from low socioeconomic backgrounds. Intervention components will be comprised of the following:

- A school curricula addressing eating cues, the influence of advertising on food choices and barriers to healthful food choices;
- A home intervention component designed to facilitate student-parent discussions regarding dietary choices, increase parental awareness of the influence of the home environment on adolescent food choices, and increase the availability of healthful food choices in the home,
- A school environment component targeting food availability, food cues and food-related incentives in the school environment.

Interventions will be implemented in the academic years 1997-1998 and 1998-1999 when students from the Class of 2004 are in their sixth and seventh grade. Formative evaluation will be conducted to determine messages and intervention strategies that are culturally appropriate and relevant.

Risk Factor Prevention for Hispanic Youth

Researchers at Stanford University have implemented a cancer risk factor prevention program targeting pre-adolescents in schools serving predominantly low-income Hispanic families. The crucial question is whether an overall intervention can have an impact on pre-adolescent obesity.

The comparatively higher prevalence of obesity among Hispanic Americans coupled with diets that are relatively higher in fat and lower in fiber may place Hispanic Americans at increased risk of cancer. The students in the study will receive interventions during both their fourth and fifth grade years. This study will include both a behavioral and an environmental component. The prevention program will include a classroom-based intervention focusing on preventing obesity by: a) increasing the perceived incentive value of adopting helpful eating and physical activity behaviors and; b) providing instruction in weight regulation skills.

Environmental intervention components will include a parent intervention coupled with the school intervention and a school food service intervention. The investigators will evaluate the efficiency of their comprehensive intervention in a cohort of 1100 underestimate from 14 elementary schools in the Alum Rock Union Elementary School District, in East San Jose, California. Students will be approximately 50 percent female, 70 percent Hispanic, 10 percent Asian, seven percent white, six percent Filipino, five percent black, one percent American Indian/Alaskan Native and one percent Pacific Islander. Seven schools will be randomly assigned to the comprehensive intervention, and the remaining seven schools will receive an attention placebo control intervention to minimize the potential for compensatory rivalry or resentful demoralization.

Assessments of children's height, weight, tricep skinfold thickness, waste and hip circumferences, food preferences, cardiorespiratory fitness and self-reported behavior, attitudes and knowledge and Tanner Stage of development will occur at baseline (4th grade), post test (5th grade), and at 10-month follow-up (6th grade). Parent interviews will occur annually. A careful assessment of effects on parents and school personnel will be completed. The primary objective is to reduce the prevalence of obesity at the end of the two year intervention. Secondary objectives include reducing intake of dietary fat; increasing consumption of low fat foods, fruits, vegetables and dietary fiber; and increasing levels of moderate to vigorous physical activity.

5-A-Day for Better Health Program

The 5-A-Day Program is an unprecedented public-private partnership between the NCI and the Produce for Better Health Foundation (PBH), a nonprofit consumer education foundation representing the fruit and vegetable industry. The 5-A-Day Program was launched at the national level in 1991 as a nationwide nutrition education effort to encourage Americans to eat 5 or more servings of fruits and vegetables every day. Several subprograms focus their efforts on influencing the diets of special population groups. To encourage better eating habits among all Americans, each state and U.S. territory has developed 5-A-Day programs to conduct research and outreach through an extensive network of community partners utilizing three key program components. The three program components are described below: infrastructure, behavioral research and evaluation, and communications research.

Infrastructure

PBH has licensed more than 1,000 industry members, representing more than 30,000 supermarkets nationwide. NCI has licensed 55 state and territorial health agencies to coordinate and deliver 5-A-Day activities through multiple community channels. In 1996, NCI expanded the Program to other federal government health promotion programs, licensing the U.S. Air Force, Army, Navy and Marine Corps, and Coast Guard, as well as the Indian Health Service. NCI has partnered with USDA's Food and Nutrition Services to promote 5-A-Day in school classrooms, cafeterias, and food assistance programs across the nation, and with CDC to collaborate with 5-A-Day at the community level.

Using a social marketing and theory driven educational approach, the community programs seek first to raise public awareness of the health benefits of eating 5-A-Day and then provides theory driven, interactive and skill building activities to show Americans how to accomplish this goal.

Statewide coalitions are instrumental in implementing the program at the community level. Coalition participants include state and county health agencies, industry (supermarkets, commodities), state departments of education and agriculture, cooperative extension, WIC, voluntary agencies (ACS), businesses, media organizations, hospitals, and state dietetic associations. Coalitions strive to reach Americans in their daily routines through advertising and retail promotions, distribution of fruit and vegetable recipes and tips in supermarkets, and sponsoring channel-specific educational efforts and community events, such as 5-A-Day activities in schools and worksites. These efforts target a variety of disadvantaged populations including: African Americans (e.g., South Carolina, North Carolina, Alabama), Hispanics (e.g., New Mexico, California, Arizona), low literacy, and persons on assistance (WIC). More than half of the states have WIC representatives on 5-A-Day coalitions.

Community efforts are evaluated within the program's research component, which consists of process evaluation and the four-year Research Grant Projects, and the one-year Evaluation Studies described below. In 1994 and 1995, the CDC funded 38 one-year Intervention Grants to address 5-A-Day project areas. The overall purpose of 5-A-Day community research is to identify effective strategies for increasing American's fruit and vegetable intake and to employ technology transfer to disseminate the research findings to society to help reduce the risk of cancer.

Behavioral Research and Evaluation

In 1992, the 5-A-Day Program was launched as a research initiative at the NCI (in contrast to the 1991 launching of the program as a nationwide nutrition education effort). The NCI's 5-A-Day Program funds research grant projects and overall program evaluation, including process and outcome evaluation. Current data show a favorable trend in both awareness and consumption. The awareness of the need to eat 5-A-Day has increased from 8% in 1991 to 39% in 1997 (NCI 5-A-Day Omnibus Survey). USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) show that fruit and vegetable intakes among adult Americans increased from 3.9 daily servings in 1989-91 to 4.4 servings in 1994. Despite the gains in adult consumption, children's

and adolescent's consumption rose from 3.1 servings in 1989-91 to 3.4 in 1994, still well below the recommendation.

In 1993, the NCI funded 9 four-year Research Project Grants with randomized controlled designs to determine the effectiveness of 5-A-Day behavior change interventions in increasing the per capita consumption of fruits and vegetables. These studies were conducted in various community settings, including schools, worksites, churches, and food assistance programs. In addition, the 5-A-Day Program has collaborated with the Centers for Disease Control and Prevention (CDC) to award 20 one-year 5-A-Day Evaluation Studies to state health agencies for fiscal year 1995, 1996, 1997 and 1998. Most of these grants targeted underserved populations: children (9 grants), low-income groups (4 grants), African-American, Latino, and Native-American populations, and low-income elderly. The Research Project Grants that involved an underserved population, overall, of 25% or more are described below by research channel. Only the research intervention is presented, as the final results are not yet published.

Four-Year Research Grants: Community Setting -Schools

Alabama

The 5-A-Day for Better Health research project at the University of Alabama at Birmingham included a 16% African-American population. This school-based intervention targeted 4th graders and their families with the 5-A-Day message to increase fruit and vegetable consumption through student and parent education, an environmental component, and industry involvement in a randomized, controlled design with children in 28 grade schools. The student education component consisted of a classroom curriculum to promote a healthy diet with school children grades 4-6 by teaching knowledge and skills for selecting foods consistent with 5-A-Day and incorporating various activities (contests, food fairs, and field trips to grocery stores). The parent component consisted of meetings with intervention nutritionists, newsletters sent to parents' homes, and child-parent cooperative activities. The environmental component involved development (poster contests) and placement of posters in classrooms, and placement of 5-A-Day stickers on food selections in the cafeteria.

Georgia

In Georgia, the “Gimme 5--The Fruits and Vegetables for Fun and Health” research project at Emory University targeted a population that was greater than 30% African-American. The school based intervention aimed to improve the dietary impact at home by increasing the availability of and preferences for produce and improve food preparation skills and parental outreach. The 4th and 5th grades in 16 schools were matched and randomly assigned within pairs to intervention and control conditions. Only the intervention schools received the school-based intervention; all schools received the media and grocery store interventions. The media and grocery store interventions were expected to potentiate the effects of the school-based components by focusing more attention on fruits and vegetables in other sectors of the community. The school-based intervention included: 1) curriculum that is participative and focused on increasing consumption at home and when eating out; 2) teacher training; 3) school food service, involving taste testings, expansion of food choices, posters; 4) family involvement:

through newsletters, homework assignments and recipes to be done by the child and parent, and; 5) videos on food acquisition, preparation skills, and demonstrations for additional family involvement.

Minnesota

The “Minnesota 5-A-Day Power Plus” research project of the Minnesota Department of Health included a 45% minority population which included significant Asian (largely Hmong), African-American, Hispanic, and American Indian populations. This elementary school-based intervention aimed to increase consumption of fruits and vegetables among school children through: food service menu changes, classroom curricula, family involvement, and industry and media support. A total of 20 urban schools were randomly assigned to intervention and control conditions. A secondary goal was to determine whether the family involvement and industry/media components of the intervention can be successfully integrated with the school-based components. Two campaigns by local TV and radio stations supplemented the school curricula. Food distributors and retailers participated by adopting classes/schools (providing food, promotional materials, and taste testings; arranging a speakers bureau for school groups; and participating in student field trips to stores and farms).

Four-Year Research Grants: Community Setting - Worksites

Arizona

In Arizona, the “5-A-Day--Healthier Eating for the Overlooked Worker” research project at the Arizona Cancer Center targeted a population that was predominantly Hispanic. This study compared the impact of interpersonal networks of peer educational programs at worksites to traditional worksite wellness programs that used impersonal communication channels. The persistence of this impact on a population of 2100 blue collar workers in 10 large public sector worksites were evaluated in a matched pair design in which all sites initially received the traditional 5-A-Day Worksite Wellness Program (a program kit for each employer's Wellness Coordinator, a campaign plan with materials, cafeteria promotions, and a speaker's bureau). After 9 months, a Health Peers Program was randomized to half of the matched pairs of worksites. This was the key intervention tested in the experimental group and involved 40 paid health peers from participating worksites trained to activate social networks. They made informal contacts with coworkers in the target population, provided nutrition information and encouraged increased consumption of fruits and vegetables. Supporting organizations included grower and retail grocer associations, individual growers, distributors and grocers; American Cancer Society; and the State Health Agency.

Massachusetts

In Massachusetts, the “Treatwell 5-A-Day Worksite Nutrition Intervention” research project based at the Dana Farber Cancer Institute included a population that was approximately 33% African-American and 33% Hispanic. The worksite intervention was based on the Treatwell Program, found to be efficacious in an NCI-funded study, but adds a family involvement component not previously studied in worksite intervention programs. The worksites were 22

community health centers that serve high-risk, low-income communities. They were randomized into 3 groups: worksite and family intervention, worksite intervention only, and control nonintervention conditions. The project was a unique collaboration between academic and community organizations. This partnership included a Comprehensive Cancer Center, State Health Agency, cooperative extension, and industry (including The Dole Food Co., Massachusetts Federation of Farmers Markets, Massachusetts Association of Roadside Stands, and a local retailer).

Four-Year Research Grants: Community Setting - Religious organizations

North Carolina

In North Carolina, the "Black Churches United for Better Health" research project of the North Carolina Department of Environment, Health, and Natural Resources targeted a 95% African-American population. Ten counties in the state, each with five recruited churches, were randomly assigned to intervention and control groups. Intervention strategies included media and point of purchase promotions, tailored 5-A-Day messages, educational sessions and increasing fruit and vegetable offerings in churches, and increasing social support via lay health advisors. The latter approach involved grocery stores and featured recipe contests, planting victory gardens, and establishing food cooperatives. Local health department and cooperative extension staff assisted in implementing these interventions. The investigators worked with the Department of Agriculture to implement a media approach that linked churches to retailers and producers in proximity to intervention sites. This project resulted in a significant change of a "one serving increase" in fruits and vegetable consumption in the intervention counties.

Four-Year Research Grants: Community Setting - Food Assistance Programs

Maryland

In Maryland, the "5-A-Day WIC Promotion Program" research project of the University of Maryland at Baltimore targeted a population that was 70% African-American. This multifaceted community-based intervention sought to increase fruit and vegetable consumption among low income women in the U.S.D.A. Special Supplemental Food program for pregnant women, infants, and children (WIC). The study used a randomized crossover design to assign 16 WIC sites to intervention and control conditions. The Program was implemented by a team of health professionals, State and Local Departments of Health, State Department of Agriculture, and the American Cancer Society. Intervention strategies included: 1) nutrition education using WIC paraprofessionals, Cooperative Extension agents, and lay counseling by trained peer group leaders; 2) print materials (reminders, calendars), and; 3) community-based family involvement and environmental enhancements (recipe solicitations, Farmer's Market coupon program, and national and local supermarket programs).

Communications Research

The national media campaign, a joint effort between NCI and PBH, spreads the 5-A-Day message to the public through media events and campaigns held throughout the year. These initiatives involve broadcast media, national spokespersons, print and special events. Annual 5-

A-Day Week (second week in September) allows a myriad of 5-A-Day participants to join forces for a week of high visibility promotions. Governors of nearly all 50 states signed Proclamations supporting the 5-A-Day effort in 1993 and 1994.

NCI's Office of Cancer Communications has adapted a social marketing model for 5-A-Day communications strategies. The Consumer-based Health Communications (CHC) model guides the research that is consistently used in the program to learn about its target audience, to track its progress, and to evaluate and study the audience's attitudes and behaviors about nutrition, fruits and vegetables, and general lifestyle and health issues.

A series of focus groups were conducted in 1994 with African-American men and women to explore perceptions about food experiences, examine benefits, barriers, and motivators to eating healthy, and to examine reactions to the 5-A-Day strategy. Results helped shape message and delivery mechanisms for activities, including radio segments for African-American listeners via partnership with NIH's National Heart, Lung and Blood Institute and its Healthbeat; media newsletter for National Minority Cancer Awareness Week; and activities at the National Council of Negro Women's annual Black Family Reunion in Washington, DC, Los Angeles, and Chicago.

Item

Breast Cancer -- Breast cancer continues to have a devastating impact on our country. In the United States, there are approximately 2.6 million Americans living with breast cancer. Each year, nearly 180,000 women are diagnosed with and nearly 44,000 women die of breast cancer. The Committee strongly urges the Institute to continue to expand breast cancer research and to devote the highest possible funding level to finding the causes and cures for this disease. (p. 112)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. SEER data indicate that breast cancer is the leading site of new cancer cases for women and, after lung cancer, the second leading cause of cancer deaths in women. An estimated 175,000 American women were diagnosed with breast cancer last year, and about 43,300 women died from the disease. Despite the significant advances in detection, diagnosis, treatment, and prevention, thousands of women continue to lose their lives to breast cancer each year. Therefore, breast cancer research remains a high priority for the Institute. The development of preventive strategies to reduce breast cancer incidence, of early detection methods, and improved therapies should be a priority for scientific and medical communities as well as for the NCI.

Statistics from the NCI's SEER Program reveal that breast cancer incidence increased 1.8% per year from 1973-1990 but has increased only 0.4% per year from 1990-1997. Overall breast cancer mortality rates have shown an encouraging downward trend, dropping 2.1% per year from 1990-1997, a finding that suggests improved breast cancer management from early detection to treatment, is having a beneficial effect. Between 1990 and 1997, breast cancer mortality

declined 2.4% in white women and shows a larger decrease during the more recent five-year period (1993-1997). The mortality trend in the 1990s leveled off for African-American women though we may be seeing a small 0.3% decline for the latest five year reporting period. The decline in breast cancer mortality during the 1990s is in contrast to increasing trends observed between 1973 and 1990 for both white women (0.2% per year) and African-American women (1.3% per year) according to data from the National Center for Health Statistics (NCHS).

We have made much progress in understanding the genetics and biology of breast cancer. We have improved technologies for detection and diagnosis, expanded the potential strategies for preventing the development of the disease, and developed more effective treatments and improved quality of life for breast cancer patients and survivors. Over the past two decades, research supported by NCI has led to many important advances in breast cancer detection and treatment. We understand more than ever before how a healthy breast cell becomes cancerous, how breast cancer spreads, why some tumors are more aggressive than others, and why some women suffer more severely and are more likely to die of the disease. These discoveries are being successfully translated into therapies that extend cancer-free survival and improve the quality of life for those continuing to live with the disease. However, despite significant advances in detection, diagnosis and treatment, thousands of women continue to lose their lives to breast cancer each year. Therefore, breast cancer remains a very high priority for the Institute. To identify and prioritize scientific needs and opportunities that are critical to facilitating progress against breast cancer, NCI established a Breast Cancer Progress Review Group (PRG) that reviewed NCI's fiscal year 1997 breast cancer research. The report of the NCI's Breast Cancer PRG, Charting the Course: Priorities for Breast Cancer Research, identifies a number of questions that still need to be answered and areas of research and care that need to be further addressed. NCI expects to use a portion of its grant funds to support high-priority applications relevant to breast cancer. We plan to give special attention to applications that address high-priority gap areas as defined by the Breast Cancer PRG, particularly those that fall within the areas of extraordinary opportunity in the NCI's Bypass Budget but fail to meet the established payline. We shall also pay particular attention to applications addressing aspects of breast cancer research that are described as high-priority and important gap areas by the Breast Cancer PRG, the complete report of which is available on line (http://wwwosp.nci.nih.gov/planning/prg/bprgtableofcontents.htm).

NCI has also been proactive in seeking coordination and collaboration with other entities with an interest in breast cancer. NCI has established the Common Scientific Outline (CSO) as a way to categorize disease specific research, including breast cancer, with respect to NCI supported science. The coding of all NCI supported research into the CSO will be built into a web accessible and searchable portfolio of NCI science being made available to the public, the Congress, the Administration, and the Cancer Community. The CSO is the platform upon which the Institute will share and compare information on research across national funding agencies allowing for enhanced collaboration and coordination of research efforts. The NCI is currently collaborating with the DoD to co-code both agencies portfolios to the Common Scientific Outline. Other cancer funders will be invited to participate in the near future.

NCI has funded and has been an active participant in the DHHS Secretary's National Action Plan on Breast Cancer. NCI staff have actively participated in all six of the priority areas

identified at the national meeting which launched the Action Plan in 1992. They have served as Working Group Co-chairs of three of six of the priority areas (Etiology, Clinical Trials, and Biological Resources), and the products of the Working Groups represent a significant contribution to breast cancer research.

NCI scientists are working closely with DoD staff to further the goals of the DoD's Breast Cancer Research Program (BCRP). This collaborative venture has ensured that unnecessary overlap and duplication between the two programs are avoided and that the two agencies' research programs complement each other and act synergistically. NCI staff members serve on the DoD's BCRP Integration Panel, a group which serves as a second-level advisory body to the program, making programmatic decisions related to program relevance and other considerations in determining funding priorities to the Army.

In addition to the Breast Cancer PRG, the NCI has solicited recommendations from other working groups focused on important areas of cancer research to assist the Institute in its strategic planning process. Through this planning process, the NCI has implemented a number of initiatives that are meant to strengthen the nation's cancer research infrastructure. *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 2001* includes descriptions of these initiatives. The initiatives are not, for the most part, disease-specific, but address problems and opportunities common to all tumors and emphasize the development of technologies and approaches applicable to many cancers.

Research Funding for Breast Cancer

The NCI portfolio of funded research projects in breast cancer is both broad and deep with over 1400 individual NCI-funded projects having relevance to breast cancer. In fiscal year 1999, NCI expended over $388 million in research related to breast cancer. In fiscal year 2000, this figure is expected to exceed $400 million for the first time. Investigator-initiated research – research proposed and conducted by scientists in laboratories and clinics across the country and here at NCI – is the wellspring of scientific discovery. Funded and sustained by a variety of NCI grant mechanisms, our investigator-initiated research is continually yielding discoveries and insights into the mechanisms and causes of breast cancer and its prevention, detection, diagnosis, treatment, control, and survival. These discoveries, and their application in interventions of all kinds, are critical to reducing the burden of breast cancer and are resulting in real progress against this disease.

Through the dedicated work of these NCI-supported scientists over the past 50 years, we stand at the threshold of understanding a great unknown – how breast cancer develops at the molecular level. Because of our continued national commitment to cancer research, we are poised to expose more rapidly than ever before the inner workings of cancer cells, their genes, and the ways in which they behave. We must push forward as quickly as possible with this work. The absolute number and pace of our discoveries, and the speed with which we bring them to bear to benefit people, are directly linked to the level of resources available to support the exploration of new leads across the cancer research continuum. Moreover, we must strive to expand our research portfolio to include a greater number of research proposals that may be somewhat riskier, highly speculative, or pursue novel paths. We also must continue to expand the

translational research that converts basic science discoveries into practical, affordable, and effective ways of restoring cancer patients to health and preventing cancer throughout our population.

As we promote innovative research, we must create mechanisms that link basic, clinical, and population-based research with state-of-the-art resources and technologies; promote collaborations among researchers inside and outside of cancer research; and draw into cancer-related research scientists from allied fields such as chemistry, biology, physics, and mathematics. By bringing together researchers from allied fields, we will galvanize the complementary knowledge these individuals possess to most quickly answer the crucial questions in basic, clinical, population, and translational research. It is under this broad scientific umbrella that discoveries in the 21st century will be made.

In fiscal year 1999, NCI's Division of Cancer Biology launched a new initiative to promote and facilitate research collaborations in basic cancer research. Limited supplemental support was made available for meetings/workshops or grant-related research activities to establish focused scientific research collaborations in novel and promising areas. DCB supported 6 collaborative research projects and 13 workshops. This program continues into fiscal year 2000.

An NCI PA solicits investigator-initiated research grant applications addressing biological issues considered critical for progress in combating breast cancer. All stages of breast cancer development from normal breast tissue to metastatic disease will be explored. The purpose of this PA is to encourage new projects focusing on the biology that underlies the development and maturation of the normal mammary gland and alterations involved in early malignant and metastatic breast cancer. Multidisciplinary collaborations between, for example, cell biologists, molecular endocrinologists, bioengineers, geneticists, and mammary pathologist, have been encouraged to apply.

To encourage translational research, National Cancer Institute (NCI) has issued a program announcement (PA) calling for grant applications for Specialized Programs of Research Excellence (SPORE) in organ-specific cancers. Applicant institutions must be able to conduct the highest quality balanced translational research on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer. SPORE applicants are judged on their current and potential ability to translate basic research findings into innovative research settings involving patients and populations. A SPORE is also encouraged to conduct research on rehabilitation and quality-of-life. A SPORE must develop and maintain human cancer tissue resources for the particular organ-site that will benefit translational research; develop extended collaborations in critical areas of research need with laboratory scientists and clinical scientists within the institution and in other institutions; and participate with other SPOREs on a regular basis to share positive and negative information, assess scientific progress in the field, identify new research opportunities, and promote inter-SPORE collaborations to resolve areas of scientific controversy.

Surveillance and Behavioral Research

Cancer surveillance—identifying and tracking trends in our national cancer burden, and monitoring the factors that influence these changes—is a crucial underpinning of our efforts to prevent and control cancer. Unequivocally, we are making real progress against cancer, and reduction in the cancer burden on people is a critical measure of that progress. Between 1990 and 1996, cancer incidence and death rates dropped for all cancers combined and for most of the top 10 cancer sites, reversing a decades-long trend of rising cancer incidence and death in the United States. These decreases are hard evidence of the wisdom of this Nation's investment in cancer research.

Appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of disease. Established in 1973, NCI's Surveillance, Epidemiology, and End Results (SEER) cancer registry program has been a world model for tracking population trends in cancer morbidity and mortality. The NCI cancer surveillance program uses SEER data to identify and study trends, track the impact of cancer on the general population, and provide information that researchers need to ask critical questions about why certain populations are affected by cancer more severely than others. SEER data have enabled us to identify environmental carcinogens, track cancer-related effects of tobacco on men and women, identify geographic areas with higher than average cancer rates, study patterns and outcomes of cancer care, and identify risk groups for research and public health intervention programs.

The SEER special studies provide a mechanism for augmenting data collection beyond the current reporting requirements and established standard data items. These studies are designed to provide more information in the broad topic areas of NCI initiatives, cancer control and prevention, the technical aspects of cancer registry operations, and surveillance. Several studies on breast cancer treatment and patient survival are underway. Data on treatment of breast cancer are being analyzed and will describe the therapy being provided to women newly diagnosed with early stage breast cancer. For example, the Health, Eating, Activity, and Lifestyle Study is investigating the independent and combined effects of height, weight, physical activity and diet, and changes in these over time, on the prognosis of women with early stage breast cancer. A detailed examination of the roles of hormones and genetic factors, as well as quality of life has been added to this study of breast cancer progression. The Ductal Cancer In Situ (DCIS) Study will obtain slides to determine whether pathology reports can be used instead of slide reviews in studies of women with DCIS. Slides will be centrally reviewed for all cases of DCIS who did not receive treatment, including surgery. A sample of DCIS cases with vague or incomplete reports will be reviewed as well as a sample of women with BCS who had a recurrence to determine whether margins were clear. If the pathology reports can be used rather than slide reviews, this would significantly reduce the cost associated with studies of DCIS. Data from these analyses will be available by Spring 2000.

Other NCI initiatives related to breast cancer surveillance and behavioral research include:

Enhancement of the Cancer Surveillance Research Program

NCI plans a number of enhancements to its Cancer Surveillance Research Program. This program includes the Surveillance Epidemiology and End Results (SEER) database, which tracks

trends in the incidence and impact of cancer in a sample comprising approximately 14% of the US population. The enhancements will largely take the form of targeted special studies permitting the development of hypotheses concerning the origins of observed trends in incidence and mortality within the population. Breast cancer is a particularly important area for emphasis, since the mortality from breast cancer differs according to ethnic group and we have little understanding of the basis for this variation. Similarly, the impact of screening on incidence, stage at diagnosis, survival, and mortality is an area of great current interest.

Cancer Intervention and Surveillance Modeling Network (CISNET)

This initiative will fund simulation and other modeling techniques to describe the impact of interventions (i.e., primary prevention, screening, and treatment) in population-based settings. Projects can focus on models describing: (1) the population dissemination of new interventions, (2) the impact of interventions on observed national trends, (3) the potential impact of a new interventions on future national trends, and/or (4) determining the impact of targeted cancer control interventions on population outcome. The first round of funding will focus on prostate, breast and colorectal cancers.

Expansion of the Breast Cancer Surveillance Consortium

NCI has expanded the Breast Cancer Surveillance Consortium (BCSC), a group of eight collaborative sites around the U.S., designed to link data from mammography centers to data from pathology laboratories and cancer registries to evaluate population-based screening mammography in the United States. This effort will identify measures of quality mammography and examine how patient, provider, and health system characteristics may influence mammography performance. Studies supported by this research effort have identified that the sensitivity of mammography to detect breast cancer may be influenced by when in the menstrual cycle premenopausal women undergo screening. Similarly, several studies have found that the performance of mammography among postmenopausal women is reduced among women who are receiving hormonal replacement therapy. These findings may have direct implications for when premenopausal women should undergo screening with respect to their menstrual cycle, and whether postmenopausal women on hormone replacement therapy should be advised to hold use of hormone replacement therapy for a short period of time before their routine screening mammographic exam.

The BCSC has led to the development of data linkages between radiologic practices, pathology laboratories, and cancer registries to obtain data on screening mammography, recommended and subsequent work up, and treatment. In addition to funding sites to collect data relevant to mammography performance, NCI has also made funds available for a Statistical Coordinating Center to provide the research expertise on complex statistical issues for analysis of these data, to serve as the central site for the repository of data for pooled data analyses, and to coordinate the development of data comparability processes for pooled data analyses.

Exploratory Grants for Behavioral Research in Cancer Control

The NCI is soliciting research grant applications from interested investigators to conduct timely, innovative, developmental, or methodological behavioral research in cancer prevention and control through a program of exploratory investigator-initiated R21 grants. This PA is intended to stimulate innovative approaches to primary and secondary cancer prevention, prevention of cancer associated morbidity, quality of life, rehabilitation, and health promotion behavioral research through a program of exploratory investigator-initiated R21 grants. It is expected that these R21 grants will serve as a basis for planning future behavioral and cancer control intervention research project grant applications (R01). The final receipt date will be October 1, 2001.

The SEER-Medicare database

This database represents the outcome of a collaborative effort of the NCI, the SEER registries, and the Health Care Financing Administration, is a large population-based source of information for cancer-related epidemiologic and health services research. This database, which contains information on cancer cases from 1986 through 1996, allows researchers to address topics such as the economics of cancer care, patterns of care from diagnosis through end of life, variation in care across diverse health care systems, and changes in cancer care over time. In 1999, 14 articles using SEER-Medicare data have been published. The focus of these papers has included comparisons of cancer care between persons with fee-for-service (FFS) coverage versus HMO care, factors that influence the reported changes in cancer incidence, patterns of cancer care, and methodological evaluations of the utility of Medicare claims for cancer surveillance. The findings from the HMO and fee-for-service comparisons are varied. In the case of prostate cancer, men with FFS coverage have better cancer-specific survival than men in HMOs, while for colon cancer, cancer-specific mortality was comparable between persons with FFS and HMO coverage Perhaps the most noteworthy conclusion from two of these studies is that there is considerable variation in treatment patterns between individual HMOs. As a result, findings from studies comparing care from an aggregation of HMOs with an aggregation of cases provided to person with FFS coverage may have limitations in the ability to extrapolate findings to all HMOs.

Cancer Surveillance Using Health Claims-based Data Systems

The NCI, the National Institute of Dental and Craniofacial Research (NIDCR), and the Agency for Health Care Policy and Research (AHCPR) are cosponsoring a program announcement encouraging submission of investigator-initiated grant applications for research to investigate the utility of health claims information as a reporting source for assessing the national cancer burden. Health claims include secondary data sources, for example, fee-for-service insurance bills, managed care encounter data, and discharge summaries. Topics addressed, could include the use of health claims information to estimate patterns of care, outcomes of care, and effects of cancer therapies. Projects in this area would help to expand the current mechanisms and resources for assessing all aspects of cancer surveillance, such as cancer screening, incidence, treatment, and outcomes.

Cancer Research Network

The NCI has established the Cancer Research Network (CRN) to encourage the expansion of collaborative cancer research among health care provider organizations that are oriented to community care, have access to large, stable and diverse patient populations and are able to take advantage of existing integrated data-bases that can provide patient-level information relevant to research studies on cancer control and cancer-related population studies. The CRN is designed to enhance research on cancer epidemiology, prevention, early detection and control in the context of health care delivery systems. The first CRN project has been awarded to the HMO Cancer Research Network, a consortium of researchers affiliated with ten major non-for-profit health maintenance organizations: Group Health Cooperative of Puget Sound, Fallon/Meyers Primary Care Institute, Harvard Pilgrim Health Care, HealthPartners Research Foundation, Henry Ford Health System, Kaiser Permanente - Hawaii, Kaiser Permanente - Northern California, Kaiser Permanente - Northwest, Kaiser Permanente - Rocky Mountain, and Kaiser Permanente - Southern California. In collaboration with the National Cancer Institute, The HMO Cancer Research Network is conducting a number of major research projects, including two related to breast cancer. One project will investigate potential reasons for the occurrence of advanced breast cancer cases among HMO members, including: (1) failure to screen, (2) failure to detect, (3) failure in follow-up, (4) biological characteristics of the tumor that make it resistant to effective screening. The study will point to innovations in health provider behavior, health care system factors or technological innovations that could result in improved effectiveness of breast cancer screening in community care settings. Another project will explore the appropriate medical management for women at increased risk for breast cancer due to family history or personal medical history. Retrospective studies, using a case-control approach, will evaluate the efficacy of early screening and prophylactic mastectomy among women at increased risk for breast cancer. This study is possible to undertake in very few settings because it requires large numbers of women and automated medical records to identify eligible subjects. It will provide important information about the efficacy of two management options for women at increased risk of breast cancer.

Quality of Cancer Care

As part of its new quality-of-care initiative, NCI has commissioned comprehensive reviews of the published literature on measures and methods for assessing patient outcomes for the major cancer disease sites, including breast cancer. The outcomes of interest include not only survival and traditional clinical endpoints, but also quality-adjusted survival (using both cancer-specific and generic quality-of-life measures), patient satisfaction, and the economic cost burden on patients and caregivers. This review, scheduled for completion in November 1999, sets the stage for a second, larger study to evaluate the strengths and limitations of the outcome measures used to date for breast and other high-prevalence cancers. Based on this literature evaluation, which will extend through fiscal year 2000, NCI will seek to identify a set of “core” outcome measures that could be employed in a range of quality-of-care analyses, including both observational studies of newly diagnosed patients and selected randomized trials.

NCI is also supporting a project which will utilize a multi-disciplinary research team to develop a simulation model which will incorporate existing knowledge on the natural history of breast

cancer, the quality-of-life of African-American women who experience various breast cancer treatments and outcomes, direct and non-direct monetary and time costs associated with breast cancer treatment, costs and effectiveness of policies and programs to increase effective screening and follow-up among African-American women. The results of this analysis will be useful to inform the optimal design of health services delivery programs and to indicate the need for priority research and service areas to ensure that targeted levels for breast cancer mortality reduction are achieved among all women in the U.S.

The National Cancer Institute (NCI) has joined other institutes in inviting research applications to focus on the unique problems of older women with breast cancer. The purpose of this broad-based program announcement is to expand the knowledge base on breast cancer in older women through studies in the fields of biology, clinical medicine, epidemiology, and the behavioral and social sciences.

Prevention

NCI is the primary supporter of the Study of Tamoxifen and Raloxifene (STAR). This clinical trial designed to see how the drug raloxifene (Evista®) compares with the drug tamoxifen (Nolvadex®) in reducing the incidence of breast cancer in women who are at an increased risk of developing the disease. Tamoxifen has been used for more than 20 years to treat patients with breast cancer. This drug works against breast cancer, in part, by interfering with the activity of estrogen, which promotes the growth of breast cancer cells. In October 1998, the U.S. Food and Drug Administration (FDA) approved tamoxifen to reduce the incidence of breast cancer in women at high risk of the disease based on the results of the Breast Cancer Prevention Trial (BCPT). The BCPT is a study of more than 13,000 pre- and postmenopausal high-risk women ages 35 and older who took either tamoxifen or a placebo (an inactive pill that looked like tamoxifen) for up to 5 years. NSABP conducted the BCPT, which also showed that tamoxifen works like estrogen to preserve bone strength, decreasing fractures of the hip, wrist, and spine in the women who took the drug. Raloxifene is a drug, taken by mouth as a pill. In December 1997, Raloxifene was approved by the FDA for the prevention of osteoporosis in postmenopausal women. It is being studied because large studies testing its effectiveness against osteoporosis have shown that women taking the drug developed fewer breast cancers than women taking a placebo. Researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting the study at more than 400 centers across the United States, Puerto Rico, and Canada.

The Breast Cancer Risk Assessment Tool is a computer program that women and their health care providers can use to estimate a woman's chances of developing breast cancer based on several recognized risk factors. The Breast Cancer Risk Assessment Tool also provides information on the drug tamoxifen. Scientists at the NCI and the NSABP developed this tool. The risk factors included in the tool are: personal history of breast abnormalities, current age, age at first menstrual period, age at first live birth, breast cancer history of close relatives, whether a woman has had a breast biopsy, and race. Other risk factors for breast cancer have been identified or proposed, but are not included in the Breast Cancer Risk Assessment Tool for two reasons: either evidence that these factors contribute to breast cancer risk is not conclusive, or researchers cannot determine how much these factors contribute to breast cancer risk as

precisely as with the factors listed above. Such risk factors include: age at menopause, dense breast tissue, use of birth control pills or hormone replacement therapy, a high-fat diet, alcohol, radiation exposure, and environmental pollutants. The Breast Cancer Risk Assessment Tool estimates a woman's risk of developing breast cancer for two time periods: over the next five years and for her lifetime. The tool compares these risks (given as a percentage) to those of a woman of the same age with no risk factors other than her age, and with the risk of women who were eligible to participate in the BCPT.

NCI is funding an initiative entitled "Regional Variation in Breast Cancer Rates in the U.S." This initiative, an RFA issued in partnership with NIEHS, stimulates further interdisciplinary epidemiologic studies to better understand determinants of regional variations in breast cancer incidence and mortality rates in the U.S. Five research studies are taking known risk factors into consideration and utilize biological markers or indicators, e.g., of exogenous exposures, individual susceptibility to environmental factors, intrinsic physiological processes or risk-related behavior, for elucidating the role of geographic-specific elements in the natural history and progression of breast cancer. The investigators are expected to meet to discuss shared scientific issues and establish collaborations. The ultimate objective of this research is to gain knowledge that could lead to effective prevention and cancer control strategies.

Physical activity, body mass index, and weight change are being intensively studied for their relationship to the risk of breast cancer. Multidisciplinary projects are attempting to assess how alcohol and tobacco use, physical activity, obesity, dietary factors, hormones, estrogen metabolism, and susceptibility factors may interact in the etiology of breast cancer. Methodologic research is assessing how best to measure physical activity during work and recreation, seasonally, and over women's lifespan.

Recent progress in understanding the genetic factors that predispose to breast cancer has allowed the identification of women at markedly increased risk of the disease (50-85% lifetime risk) due to an inherited mutation of a breast cancer gene BRCA1 or BRCA2 or a family history of breast cancer that suggests a mutation may be present. Despite the high risk, cancer prevention options for these women have been limited to observation and early detection, chemoprevention with tamoxifen, or prophylactic surgery to remove breasts and/or ovaries before disease develops. Little information has been available about the efficacy of these interventions to guide the cancer prevention decisions facing these high-risk women.

Bilateral prophylactic mastectomy has been offered as a prevention option to women at high risk of breast cancer, despite case reports of cancers occurring after surgery. To evaluate the efficacy of preventive mastectomy, NCI-sponsored researchers studied the long-term outcomes of surgery in 639 women with a family history of breast cancer who had undergone prophylactic mastectomy between 1960 and 1993. For both the 214 women at high risk (compared to their sisters without surgery) and the 425 women at moderate risk (compared to population-based statistics), prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90%.

Prophylactic removal of the ovaries has been recommended for women at inherited risk of breast and ovarian cancer on completion of childbearing to decrease the risk of ovarian cancer.

To explore whether prophylactic oophorectomy lowers the risk of breast cancer among women at inherited risk of breast and ovarian cancer, NCI-sponsored researchers from five North American medical centers compared the incidence of breast cancer in 43 women with BRCA1 mutations who had undergone prophylactic oophorectomy with that of 79 women with similar mutations who had not had this surgery. They found that prophylactic oophorectomy reduced the risk of breast cancer by about 40% for all women with BRCA1 mutations and that risk reduction increased over time from surgery. The use of hormone replacement therapy following prophylactic oophorectomy did not negate the observed reduction in breast cancer risk.

These studies are of major importance to the health care of women at markedly increased risk of breast and/or ovarian cancer due to an inherited mutation of BRCA1 or a strong family history of breast and/or ovarian cancer because they provide a scientific basis for difficult cancer prevention decisions. Clearly, further research is needed to replicate these findings and to explore other aspects of prophylactic surgery, including optimal surgical techniques, hormone replacement and chemoprevention following surgery, and the public health implications of these interventions among targeted risk groups.

Other specific NCI initiatives related to prevention of breast cancer include:

Clinical Trials in Prevention and Early Detection

The NCI expects to fund a number of clinical trials in the area of breast cancer prevention. It is likely that these trials will test the efficacy of pharmaceutical compounds and dietary constituents, singly and in various combinations in preventing cancer. These multicenter studies will be performed by groups with expertise in clinical trials and access to large numbers of subjects at risk for breast cancer. The NCI will also fund other trials assessing biomarkers of risk for prevention and early detection.

Rapid Access to Prevention Intervention Development (RAPID)

A program analogous to RAID, for discoveries that might be useful for cancer prevention. The aim is to support the preclinical development of chemopreventive agents and clinical development through Phase I studies by assisting investigators in accomplishing the rate-limiting tasks in the process of bringing discoveries from the laboratory to the clinic. This assistance is provided through the use of NCI chemopreventive agent development contracts and facilitated by direct consultations between the originating laboratory and NCI staff.

Imaging

Over the last quarter century, refinements in imaging technology have substantially broadened the range of medical options. Current imaging tests now provide much clearer and more detailed pictures of organs and tissues than were possible previously. Imaging already has had a lifesaving effect in detecting some early cancers. X-ray mammography, for example, has saved the lives of many women by revealing the presence of very small cancers before they could be detected by physical examination. Computed tomography (CT) and ultrasound permit physicians to guide long, thin needles deep within the body to biopsy organs, often eliminating

the need for an open surgical procedure. CT can reveal whether a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs; important information that can help guide treatment choices.

Three years ago, NCI recognized the great untapped potential that imaging technology holds for cancer and identified it as an area of extraordinary opportunity. With this designation, we began a three-year effort aimed at significantly advancing imaging to more fully exploit its promise for cancer research and care. By establishing an Imaging Working Group, we stimulated constructive communication among experts from diverse disciplines who have advised NCI about how we can quickly and effectively move imaging research forward. The efforts of this group helped us define research needs and opportunities. In the past year, we launched a national network to evaluate diagnostic imaging technologies. We also have established several small-animal imaging research centers. Still, we have much important work to do before the full promise of the imaging sciences is realized for cancer. Having laid the groundwork, we now will target tangible improvements in cancer detection, diagnosis, and treatment – results that will provide real clinical benefits for people with cancer and those at risk.

Important advances in imaging systems are being applied to the detection of breast cancer. The NCI is funding breast imaging with elastography, MRI and magnetic resonance spectroscopy, a number of ultrasound techniques, positron emission tomography (PET) and single photon emission computed tomography using a number of compounds designed to look at molecular biological and metabolic characteristics, and optical technologies emphasizing the use of the near-infrared region of the spectrum. A multi-center, international clinical trial in the use of MRI in the detection of breast cancer is being funded. Nearly four hundred patients have been accrued at 10 centers in this trial to test MRI as a tool to decrease the number of false-positive x-ray mammograms that lead to biopsy. NCI is also funding a multi-center trial of breast MRI as a screening test for breast cancer in women at high-risk for breast cancer. The NCI initiated funding in fiscal year 1999 a large, 5-year project combining the development of four of the above technologies, which will all be tested in a group of interested women arriving for mammography. Ongoing research in digital mammography, in 11 projects, includes x-ray source and digital detector development, image optimization and interpretation studies, and studies of impact and cost.

NCI is actively pursuing the identification of factors that can be utilized to estimate a woman's future risk for breast cancer. One such factor being brought under study is the density of breast tissue as seen on mammograms. Increase density indicates a preponderance of glandular tissue over fatty tissue, and appears to be predictive of increased cancer risk. Current research focuses on developing accurate measures of breast mammographic density and correlations of these measures to breast cancer risk. NCI is also providing support for a project to develop novel mathematical models that build on known physiological and epidemiological characteristics of breast cancer, along with preliminary information about test performance characteristics and costs to estimate the cost-effectiveness of new and emerging breast imaging technologies, such as MRI and digital mammography.

Other specific initiatives related to imaging include:

Diagnostic Imaging Network

The NCI has funded a national multi institutional network for cooperative studies in diagnostic imaging. This network will develop productive interfaces with industrial sources of new imaging technology and will have the capacity to perform both limited institution pilot studies and full-scale randomized controlled trials to assess the value of imaging innovations in the practice of oncology. NCI expects that studies in breast cancer will form an important part of the research agenda of this network, aided by collaborative arrangements with the clinical cooperative groups.

Development and Testing of Digital Mammography Displays and Workstations (PA).

Digital Mammography is one of the most promising research areas for improving early detection of breast cancer; however, current soft-copy (i.e., video) display systems remain an impediment to full realization of the potential of digital mammography. Extensive effort is required for the successful development, testing and implementation of digital mammography displays and workstation design for image interpretation. Studies are needed to objectively evaluate display technologies for mammographic imaging. High resolution display technologies providing high spatial and contrast resolution, high luminance, high dynamic range and wide viewing angle at reasonable cost need to be developed. Modeling of radiologists' viewing and work patterns in both screening and diagnostic environments will discover critical parameters of work flow to guide workstation design. Psychophysical studies of the effect of display parameters on detection and discrimination of diagnostic features in mammograms will allow optimization of workstation design. This initiative is intended to advance the state of the art in digital mammography displays and workstation design to facilitate clinical acceptance and implementation of digital mammography for improved breast cancer diagnosis. The PA will solicit research and development in three critical areas in digital mammography: 1) Softcopy Display Hardware; 2) Workstation Software and Design; and 3) Image Perception. Eleven applications were received in the first cycle. Applicants proposed the improvement of monitors, the creation of workstations and their testing in the clinical setting. The first awards under this Program Announcement will be made after the next NCAB meeting.

Four manufacturers have produced prototype test digital mammography units. Limited clinical trials are underway for the purpose of securing FDA permission to market the devices. The FDA has withdrawn its original (1996) Guidance, “Information for Manufacturers Seeking Marketing Clearance of Digital Mammography Systems,” and has not completed a new Guidance, so the approval path for digital mammography devices is not clear. NCI believes that it is important to support research aimed at optimizing digital mammography technology and to support clinical trials. Data from the clinical trials currently underway will help determine whether and what kind of large-scale clinical trials may be necessary. The goal is to determine whether digital mammography is better than conventional film-screen mammography, and if it is, of what kind and how large the improvements are.

To promote large-scale testing of women to quantify the increased detection success of digital mammography relative to film/screen mammography, NCI staff members have discussed trial design internally and developed recommendations. This group has reviewed the current protocols of digital mammography trials funded by industry or government agencies, observing their progress in patient accrual. The NCI-funded Digital Imaging Network (ACRIN) was asked to develop a protocol and accompanying budget to carry out a large-scale trial. The first draft of the protocol has been completed and submitted to NCI for review, discussion, and feasibility determination. By spring, 2000, the NCI will decide how this trial fits into its overall priorities and funding plans.

Early Detection Research Network

The NCI is establishing a multi institutional consortium to develop sensitive and specific tests for the early detection of cancer. This Network will link centers of expertise in tumor biology, diagnostics technologies, and clinical-trials methodology in academia and industry to develop high-throughput assays suitable for clinical testing. The Network will have the capacity to establish estimates of the operating characteristics of candidate assays as early-detection tools. NCI intends that breast cancer should be one focus of activity within the new Network. To expedite the discovery and development of more sensitive and specific markers for early disease, NCI will also establish links between activities of the Network and programs in academia and industry that are developing libraries of all known secreted proteins in mammalian cells.

The consortium will have three components -- Biomarkers Developmental Laboratories, Biomarkers Validation Laboratories, and Clinical/Epidemiologic Centers. A Request for Applications (RFA) for the Biomarkers Developmental Laboratories was issued in the NIH Guide in January 1999. A second RFA was issued in March 1999 to establish the Biomarkers Validation Laboratories; simultaneously, a third RFA was issued to establish the Clinical and Epidemiologic Centers. The RFA for the Data Management and Coordinating Center was issued in April 1999. While the major thrust of the Network will be on cancers of the prostate, breast, colon, lung, ovary, and upper-respiratory tract, applications on other organ sites will also be accepted for review.

Clinical Trials in Prevention and Early Detection

The NCI expects to fund a number of clinical trials in the area of breast cancer prevention. It is likely that these trials will test the efficacy of pharmaceutical compounds and dietary constituents, singly and in various combinations in preventing cancer. These multicenter studies will be performed by groups with expertise in clinical trials and access to large numbers of subjects at risk for breast cancer. The NCI will also fund other trials assessing biomarkers of risk for prevention and early detection.

Epidemiology and Genetics

Dramatic scientific advances have led to new and fundamental insights into the causes of cancer. Fueled by conceptual and technical breakthroughs, the often breathtaking pace of scientific discovery has engendered a tremendous sense of optimism among cancer researchers that new

avenues will be found to detect, treat, and prevent cancer. Nowhere is this sense of promise greater or the potential implications more profound than at the interface of the fields of epidemiology and genetics. By marrying the epidemiologic approach – study of the distribution and causes of cancer in human populations – with cutting-edge genetic and related molecular technologies, we will be able to:

- Identify genes that predispose people to cancer (cancer susceptibility genes) whose pathways of action will point to previously unsuspected environmental carcinogens, including those related to lifestyle exposures.
- Detect the slight to moderate elevations of risk resulting from certain types of exposures by studying genetically susceptible subgroups.
- Design new approaches to diagnose, prevent, and treat cancer based on an understanding of how genes modify and interact with environmental exposures.
- Quantify cancer risks associated with gene-environment interactions, which will direct individual and public health strategies aimed at preventing and controlling cancer.

The importance of lifestyle and other environmental exposures as causes of cancer is unquestionable. The pivotal role of environment is reflected in the substantial variation in cancer incidence around the world, and in the changes in risk observed among groups that migrate and become acculturated in the host country. Furthermore, epidemiologic research has succeeded in identifying a wide range of cancer-causing exposures, including tobacco use, dietary components, sunlight, ionizing radiation, environmental chemicals, infectious agents, obesity, exercise, hormones, and reproductive factors. Nevertheless, the causes of many cancers remain elusive. While better approaches to measuring exposures will provide new insights, it is clear that the environment represents only part of the equation in determining who will get cancer. It also is important to understand cancer susceptibility. For example, why does one person with a cancer-causing exposure (such as smoking or infection with human papillomavirus) develop cancer, while another does not?

Viewing such questions through the lens of genetics promises to provide insights into these apparent paradoxes. The scientific investment in cancer genetics, initially focused on the intensive study of rare cancer-prone families, already has paid huge dividends. These studies have opened a unique window into the basic mechanisms of cancer, with benefits extending well beyond the rare families from which they were derived. This is because the genes identified by these studies are altered forms of normal genes involved in key biochemical chains of events (pathways) controlling fundamental cell processes. It has become clear that these same pathways contribute to the development and progression of the more common, non-hereditary forms of cancer. Yet even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified by other genetic and environmental factors. There is mounting evidence that one's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures. Opportunities now exist to determine how variations in these genes combine with environmental and other factors to induce cancer in the general population.

Three years ago, we identified cancer genetics as an area of extraordinary opportunity. We recognized that to exploit fully this area's potential – to move it forward at the accelerated pace that accumulated knowledge and powerful technological advances now permit – new initiatives

were needed. Many of today's new opportunities in the area of genetics are a direct benefit of these scientific investments. For example, NCI's Cancer Genome Anatomy Project (CGAP) has resulted in the discovery of approximately 50,000 new genes. New technologies have permitted scientists to determine which genes are expressed (active) in normal and cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as environmental agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public data bases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome.

NCI expended over $80 million in fiscal year 1999 for research related to breast cancer genetics. In addition, NCI has made a major investment in epidemiologic studies designed to clarify breast cancer risk factors. Such studies are assessing the role that environmental and chemical exposures, including alcohol and tobacco, may play as well as the potential etiologic importance of radiation, endogenous hormones, familial/genetic factors, and host/lifestyle factors such as physical activity and diet/nutrition. Of particular interest are studies on the role of various genetic variations, particularly among different ethnic groups, in the enzymes that metabolize steroid hormones or environmental agents. Other studies are attempting to improve techniques to measure exposures applicable to better defining breast cancer risk factors. Such efforts include methods to better assess nutritional intake and physical activity, define the genetic epidemiology of breast cancer, evaluate gene-environment interactions, and predict outcomes following a diagnosis of breast cancer.

PDQ, NCI's comprehensive cancer database, contains peer-reviewed summaries on cancer treatment, screening, prevention and supportive care. The new PDQ Cancer Genetics Editorial Board, consisting of experts in the areas of epidemiology, primary care, ethics, law, psychology and the social sciences, as well as medical genetics, develops and maintains information summaries pertaining to the rapidly growing field of cancer genetics. Soon to be released will be a comprehensive guide to the use of genetic information in the care and counseling of individuals and families at a high risk of breast and ovarian cancer related to the presence of breast cancer gene mutations or a strong family history of breast and/or ovarian cancer. This guide will help primary care physicians, nurses and cancer specialists to appropriately use and interpret complex genetic information and test results for individuals and families concerned about breast cancer.

NCI has a broad and wide-ranging research program of laboratory and epidemiologic investigations into the links between breast cancer and exposures to pesticides, air pollution, drinking water contaminants, electromagnetic and ionizing radiation, lifestyle and other factors. Environmental studies are especially challenging. Because such exposures are indirect and experienced passively, and often they occurred a long time in the past, it is difficult to quantify the long-term dose to any individual, who may not know whether and to what extent they were exposed to any pollutant. In addition, pollutants are ubiquitous and occur in the ambient environment at very low levels. Exposure is hard to measure accurately, and low levels of exposure may be associated with only small increments in risk, also hard to assess statistically. Biomarker approaches (genetic, molecular, cellular, tissue or organ-specific) are one way to assess internal dose, and are a major thrust of current research work. There has been particular

interest in identifying markers of cancer risk; for example, for detecting and quantifying influential environmental exposures, as indicators of mechanisms relating exposures and cancer, or as measurements of individual susceptibility to cancer.

A number of research studies are addressing the higher breast cancer rates in various areas of the United States. Among these projects, and in response to concerns of Long Island, NY residents about higher than average breast cancer incidence, the NCI with NIEHS undertook an extensive breast cancer case-control study. The study is examining the association of breast cancer risk with exposures to contaminated drinking water; indoor and ambient air pollution, including pesticide levels in household dust; electromagnetic fields; and hazardous and municipal wastes.

Several recent studies suggest that some organochlorines (commonly used as pesticides) affect estrogen production or metabolism and increase mammary tumors in animals; human studies are inconsistent to date. NCI is conducting case-control and cohort studies in numerous areas that will address this question; chemicals that are being measured in human serum and adipose tissues are DDE, PCBs, and PAHs. NCI and CDC are jointly following a group of farm families accidentally exposed to high levels of PBBs during the 1970s to look at a variety of health outcomes, including risk for breast cancer. Five centers that are collaborating in research seeking reasons for the increased breast cancer rates in the Northeast/mid-Atlantic U.S. are pooling data and analyses to investigate the role of organochlorine pesticides in breast cancer risk.

NCI is funding an initiative entitled "Geographic Information System for the Long Island Breast Cancer Study Project." A Geographic Information System (GIS) is a powerful computer mapping data management and analysis tool for integrating diverse sources of information that have one common element: they can be referenced to a location on the earth's surface. The purpose of this initiative is to develop, test, and document a GIS-based decision support system for investigating the potential relationships between breast cancer and estimated exposure to environmental contamination on Long Island. It will support both temporal and spatial research so that environmental factors and cancer risks can be examined as they vary over time and space.

In collaboration with NIOSH/CDC and other NIH institutes, NCI is supporting two Requests for Applications and a Program Announcement to support new research on exposure measurement, elucidation of low levels of exposure, farm worker surveillance for pesticide and herbicide exposures, and development of biomarkers for environmental and occupational studies, including breast cancer.

In 1999, the NCI co-sponsored a three-day workshop with the NIEHS on the "Role of Human Exposure Assessment in the Prevention of Environmental Disease," to discuss the current status of methods and approaches and to identify future strategies for advancing this area. Proceedings of this workshop will be prepared for publication. In conjunction with the workshop, NCI organized and sponsored an ad hoc advisory group meeting of experts to elicit recommendations for research directions and needs relating to the environment and cancer that could be addressed during the next five years.

Research priorities that have been identified also include improving the accuracy of our measurement and estimation of exposure, particularly if historical, to environmental agents and expanding our approaches to study design and analysis for conducting environmental research that focuses on gene-environment interactions. This priority area will be encouraged and supported through a Request for Applications to be issued in collaboration with NIEHS in 2000. This work has direct application to enhancing breast cancer research.

Exposure to estrogen produced by the body clearly raises risk of breast cancer. Reproductive factors that may affect levels of estrogen and other hormones are receiving intensive study with regard to breast cancer risk. Efforts are being made to measure or estimate the timing of estrogen exposure, especially during periods such as menarche and menopause. Numerous studies are addressing estrogen metabolism, estrogen and progesterone receptor levels, and excreted estrogens for potential relationships to breast cancer risk.

The incidence rates of breast cancer are substantially lower in Asian countries than in the U.S. A possible explanation is that Asian women consume much greater amount of soy foods than do Caucasian women. Isoflavonoids, present in soy foods, are structurally similar to estradiol. It has been hypothesized that isoflavonoids may influence breast cancer risk. Overnight urine samples collected from women participating in a cohort study in China were analyzed for major isoflavonoids. Levels of these isoflavonoids in the urine were substantially lower among women with breast cancer than controls. The result suggests that a high intake of soy food may reduce breast cancer risk and warrants further study as a potentially preventive intervention.
Obesity, body mass index, body fat distribution ("apple" versus "pear"), weight change over the lifespan, and physical activity are being intensively studied for their effect on breast cancer incidence, prognosis, and mortality. A broad range of dietary factors is also under study, with several projects focusing on unique dietary influences in ethnic and/or migrant groups, such as African-American, Hispanic, Native Hawaiian, and Asian-American women. Specific dietary/nutritional factors of interest include dietary fats, alcohol consumption, and caffeine. Vitamins and other antioxidants consumed in the diet are being studied for potential protective effects. Future questions of interest are whether specific dietary constituents that differ between ethnic groups can be shown to affect breast cancer risk, and methodologic studies are needed to improve the accuracy of our assessment of diet and of social and behavioral influences on dietary constituents.

Experimental evidence suggests that insulin-like growth factor (IGF)-I influences proliferation of breast epithelial cells and is thought to play a role in breast cancer. Plasma concentrations of IGF-I and IGF binding protein 3 (IGFBP-3) were measured in a nested case-control study. Premenopausal women with elevated levels of IGF-I had a 2-fold risk of breast cancer. The risk increased after adjustment for plasma IGFBP-3 concentrations among women taking tamoxifen. It remains to be determined whether baseline IGF-I concentrations can predict risk or whether IGF-I can serve as an intermediate endpoint in chemoprevention trials.

Ionizing radiation in high doses is a well-established risk factor for breast cancer. Current research focuses on the specific effects of diagnostic, therapeutic and occupational exposure to ionizing radiation in established cohorts such as X-ray technologists, ataxia-telangiectasia carriers, and A-bomb survivors, with multidisciplinary investigations of genetic susceptibility to

radiation carcinogenesis and the interactions of radiation dose, hormonal factors, and genetic factors. Non-ionizing radiation (electromagnetic field or EMF) exposure has been hypothesized to affect breast cancer risk through changes in melatonin levels that affect estrogen secretion. Current research is measuring EMF exposure in several cohorts, including teachers in California, nurses in several areas of the U.S., and women included in the Long Island Breast Cancer Study Project.

The discovery that alterations in the BRCA1 and BRCA2 genes are associated with inherited breast cancer is extraordinarily important and has fueled many research projects. In particular, there is great interest in the molecular screening of BRCA1/2 genes as markers for breast cancer risk and in assessing knowledge and attitude toward genetic testing among women at increased risk of developing breast cancer because of a potential family history. A number of research projects are using tailored information on BRCA1/2 testing to design materials for counseling and further testing or other preventive strategies. It is estimated that 2-3% of the Ashkenazi Jewish population carries one of three prominent mutations in either BRCA1 or BRCA2. Besides BRCA1/2, other molecular markers being tested as identifiable risk factors in selected populations of women include p53, ras, HER-neu, and a variety of receptors and enzymes known as kinases.

Investigators at the University of Michigan will be studying colon cancer in Israel by a 4,200 person case-control study. They will focus on APC and the mutation at I1307K, which predicts near mutations. They also will study GSTM1, NAT2, and replication error phenotyping. The specific aims of the study are to 1) measure colon cancer risk associated with this polymorphism; 2) identify effect modifiers of the pathogenesis (other genetic and environmental factors); 3) determine the mutational spectra of APC in relation to colon cancer risk factors; and 4) establish a repository for future studies.

NCI-supported investigators at the New York University Medical Center in collaboration with investigators in Israel have launched the Jerusalem Perinatal Study. This is a population-based research bank based on mothers, fathers, and offspring. In 1964-76 all Jewish births were surveyed, as were all births to Arab residents of West Jerusalem. Demographic data were recorded on the parents, infant deaths, congenital malformations, admissions to hospitals, and obstetric complications. Approximately two- thirds of the Jews were refugees or their offspring from Morocco, Algeria, Tunisia, Egypt, Iraq, Iran, Turkey, Yemen, Syria, or Lebanon. Specific subsets of the mothers were interviewed in 1966-68 and 1975-76, adding information on consanguinity, antenatal health, body size, smoking, fertility, gynecologic variables, and contraceptive use. After an average of 27 years (range 21-33) most offspring have completed their compulsory military service. This cohort may be one of the largest to include ethnic ancestry with obstetric and social data, which can link siblings and parents. The investigators propose to link this database with Israel's Cancer Registry for follow-up studies of malignancies, as the parents and offspring age, and to prepare for the potential use of this cohort for cancer prevention trials. Linkage in 1999 identified malignancies diagnosed to the end of 1996, including an estimated 1846 cases in the 34,900 mothers and 485 in the 92,500 male and female offspring. They estimate there will be 440 cancers of breast and 122 of ovary, half of them to women of non-European origin. Focusing on breast cancer in mothers, they will test for effects of gender of first offspring and explore ethnic differences in the effects of these and conventional

risk factors. They will question whether changes in incidence of breast cancer and or other cancers can be predicted by births of offspring with major or minor birth defects, including neural tube defects and Down's syndrome, or by certain obstetric outcomes, including preeclampsia. The results may identify women who would benefit from intensive screening or new clues to the etiology of breast cancer.

NCI investigators are collaborating with researchers from the International Institute of Fertility, Ra'anana, Israel on a study of BRCA1/2 mutations among Israeli Ashkenazi, non-Ashkenazi, and Arab male breast cancer patients. The study detected mutations in BRCA1or 2 in at least 17% of the Jewish patients, but none in the Arab patients. A specific BRCA2 mutation in two men of Sephardic Jewish decent was observed , which is the first time this mutation has been detected in this ethnic group. Plans are underway to follow-up on this observation by sampling a larger number of Sephardic men with breast cancer.

On May 20, 1996, the Ministers of Health of Cyprus, Egypt, Israel, Jordan, and the Palestinian Authority formed a historic partnership, with the official signing in Geneva, Switzerland, of the Middle East Cancer Consortium (MECC) agreement. NCI played a major role in orchestrating the agreement. NCI's role in the establishment of MECC is another of the Institute's ongoing efforts to support and encourage cooperation among cancer researchers and practicing oncologists in the Middle East region. The aims of MECC are to increase knowledge about cancer and to decrease its burdens for the people of the Middle East. To date MECC has funded through its Small Grants Program some 35 research projects conducted by scientists in the region. More than half of the funds provided through this program have supported research projects involving more than on MECC signatory thus encouraging and enabling scientific cooperation in the Middle East.

Among the research projects funded via NCI's support of the MECC Small Grants Program are 6 projects related to breast cancer in the region. One project involving scientists from Israel, the Palestinian Authority, and Cyprus seeks to characterize the mutational spectrum in BRCA genes in individuals at high risk for breast and ovarian cancer. A second project involving an Israeli-Jordanian collaboration involves gathering family data and genetic testing for BRCA mutations in 94 families of cancer patients in Jordan, the Palestinian Authority and Israel. A third project being conducted by scientists in Israel seeks to characterize BRCA mutations in Palestinian women where there has been a steep rise in breast cancer over the last decade. This group has recently analyzed 199 Ashkanazi and 44 non-Ashkanazi Jews with breast cancer and found that 13.5% of all patients carried one of three mutations in BRCA1 including non-Askanazi Jews of Iraqi origin. A distinct mutation in BRCA1 was characterized as a founder mutation in Yemenite Jews. In the coming year, MECC intends to issue a call for proposals and to fund pilot studies specifically addressing the epidemiology of breast cancer in the Middle East. NCI funds will be used to support these studies, and it is hoped that they will lead to more extensive collaboration on this topic between scientists in the Middle East and the NCI.

Other specific NCI initiatives related to epidemiology and genetics include:

Interdisciplinary Studies in the Genetic Epidemiology of Cancer

This initiative was funded during the past year. The objective of the initiative is to provide support to multisite, cooperative research projects by multidisciplinary teams of investigators working to collaborate within the common theme of the genetic epidemiology of cancer. Particular emphasis will be placed on etiologic mechanisms underlying the interaction of genetic and epidemiologic risk factors for cancer susceptibility. The effect on cancer susceptibility of age-related changes over the lifespan, and the genetic factors leading to older age at onset of cancer are also of interest. It is anticipated that this initiative will provide fundamental contributions to the identification and characterization of susceptibility genes for breast cancer and cancers at other sites and to the understanding of the interaction of these genes with known epidemiologic risk factors.

The Cancer Genome Anatomy Project (CGAP)

This project's central goal is the discovery of all genes expressed in targeted cancers and associated premalignant conditions (the Tumor Gene Index, TGI). Information gained by the analysis of breast-specific libraries will have wide applicability to development of more effective ways of diagnosing, detecting, treating, and preventing breast cancer. Related projects include the Cancer Chromosomal Aberrations Project, which seeks to integrate the cytogenetic and physical maps of the human genome, to generate a repository of BAC clones arrayed across the genetic and physical map, and to develop a publicly available database displaying this clone repository and providing a platform for correlation with other databases of chromosomal aberrations, as well as clinical and histopathological information.

Also related to CGAP is the Genetic Annotation Initiative (GAI), which will explore, develop, and then apply technology for the identification and characterization of genes important in cancer. Based on the gene discovery program in CGAP, the GAI is currently exploring the application of multiple technological approaches to searching the 3'UTR of genes for sequence variation. Once identified and confirmed, these variants will be put into public databases maintained by NCBI's dbSNP and the CGAP Web resources. Other support the development of technologies for high-throughput molecular analysis of the changes associated with cancer and the development of full-length cDNA clones of genes expressed in cancers. Current plans call for an expansion of the rate of gene discovery in the TGI by supplementing breast cancer SPOREs and other grantees to collaborate with CGAP investigators.

Cancer Genetics Network

This recently organized multicenter consortium will be a platform for studies of genetic susceptibility. It will serve as a vehicle for intervention studies, education programs, and gene discovery. To accomplish these goals, it is creating a registry of individuals at high risk for cancer. These individuals may serve as probands for the identification of families or as participants in other types of studies of cancer susceptibility. The Network will provide registry participants with relevant information about cancer predisposition and will facilitate access to studies focused on early detection and prevention. This year the Network is implementing pilot projects, recruiting participants into the registry, and developing operating procedures. The Network is planning activities to publicize the procedures by which the research community may gain access to its resources.

The Cooperative Family Registry for Breast Cancer Studies (CFRBCS)

The Cooperative Family Registries for Breast and Ovarian Cancer Studies, initiated by the National Cancer Institute in 1995, represent a comprehensive and collaborative research infrastructure established to facilitate interdisciplinary studies in the genetics and epidemiology of cancer. The institutions participating in this international initiative will a) collect family history information, epidemiological and clinical data, and biological specimens from individuals and patients with a family history of breast and breast-ovarian cancer and related syndromes ascertained from a variety of populations within and outside the United States; b) collect follow-up data on treatment, morbidity and mortality from participating families; c) establish both local and centralized databases; d) provide a prospective resource for population-based and translational breast and ovarian cancer research; and e) support the development of new study designs and analytical approaches in the genetic epidemiology of cancer through the use of comprehensive data sets. This registry provides biological specimens with associated family history, clinical, demographic and epidemiologic data from participants with a family history of breast cancer, breast/ovarian cancer, or Li-Fraumeni syndrome, and their relatives. The CFRBCS's repository is particularly suited to the support of interdisciplinary and translational breast cancer research.

The Family Registry infrastructure makes possible the characterization of breast and ovarian cancer susceptibility genes in terms of their penetrance and distribution in the general population. In addition, correlations between genes and clinical characteristics in these forms of cancer are being studied, and the effects of modifier genes, environmental exposures and/or lifestyle factors (such as diet, physical activity and hormonal exposure) on cancer risk are being assessed. Such research requires the collection of detailed genetic and epidemiologic data from extremely large collections of families. The results are expected to lead to important public health recommendations for populations at risk. In addition, prospective follow up will provide important information on survival, morbidity and mortality in populations at high risk for cancer, are likely to contribute essential information relevant to the design and choice of appropriate preventive and therapeutic strategies.

Four of the NCI-supported Cancer Family Registries for breast cancer have received funds for the accrual of both population and non-population-based Ashkenazi families and the testing of mutations in *BRCA1* and *BRCA2*. This collection is an integral part of the registry activity, and has supported collection of a comprehensive set of epidemiologic and molecular data and related biospecimens from an high-risk population in need of preventive strategies. When completed, this will constitute one of the largest and most complete data sets and biospecimen collections currently available for Ashkenazi families. With correction for ascertainment approaches, the pooled data will be analyzed to look at mutation-specific penetrance. This data set is particularly amenable to study of gene-gene and gene-environment interactions. In addition, non-*BRCA1/2* families will be studied to look at other highly penetrant genes. In addition, a case-control study utilizing the accumulated resources of the Cancer Family Registries for breast cancer will be conducted. Cases will be women of Ashkenazi descent affected with breast cancer who have germline mutations in either *BRCA1* or *BRCA2*.

Other currently supported studies include molecular epidemiologic investigations of heritable breast cancer, comparative assessments and validation of mutational analysis technologies, studies of the molecular pathology of familial and sporadic breast cancer, and studies on the reduction of distress among family members of women at high genetic risk for breast cancer who receive cancer risk counseling and group psychotherapy.

Clinical Epidemiologic Studies in Hereditary Breast/Ovarian Cancer

With increasing public awareness of genetic contributions to cancer risk and the commercial availability of testing for mutations predisposing to breast and ovarian cancer, women at inherited risk for these cancers must make decisions about preventive interventions - and often cancer-directed therapy - with only limited scientific information about the natural history of disease associated with predisposing mutations, the efficacy of prophylactic surgery and other preventive measures, and the appropriateness of standard oncologic care for cancers developing in mutation carriers. While prospective studies will eventually provide definitive answers to these questions, there is an immediate need to address these issues through retrospective studies based on existing resources such as tissue banks and high- risk clinic registries and through concurrent studies added to ongoing clinical or epidemiologic research projects. This initiative seeks to enhance informed decision-making among women at hereditary cancer risk by strengthening and expanding the scientific knowledge about preventive and therapeutic options. Funding will be made available for innovative epidemiologic studies, which address clinical issues facing women with inherited predisposition for breast and/or ovarian cancer. Mechanisms to be utilized include investigator-initiated grants (R01s) and competing supplements to existing NIH-funded research project grants (R01s, P01s) or cooperative agreements (U01s, U10s).

Treatment

A new web site at the NCI helps women consider whether to enter a clinical trial for the treatment of their cancer (http://cancertrials.nci.nih.gov). Launched in May 1998, the web site quickly helps women and their doctors sort through the hundreds of research studies under way on breast cancer to find those of interest to them. The NCI's PDQ database contains descriptions of over 300 clinical trials for breast cancer including 187 NCI-sponsored trials. Of these, 100 are Phase I trials in which novel approaches to dealing with breast cancer are being tested for safety and 23 are Phase III trials representing interventions that are closest to general medical practice.

Drugs used in chemotherapy use different ways to stop tumor cells from dividing so they stop growing or die. Peripheral stem cell transplantation may allow the doctor to give higher doses of chemotherapy drugs and kill more tumor cells. It is not yet known which regimen of chemotherapy followed by peripheral stem cell transplantation is more effective for breast cancer. One high priority NCI-sponsored phase III trial aims to compare the effectiveness of combination chemotherapy plus peripheral stem cell transplantation or bone marrow transplantation in treating women who have stage II or stage IIIA breast cancer.

Other initiatives in related to breast cancer treatment include:

Early Therapeutics Development with Phase II Emphasis

Through an RFP, NCI is seeking organizations or consortia with the capabilities and facilities to provide a resource for the conduct of Phase II and early clinical trials of NCI-sponsored agents, to evaluate biologic effects of these agents on their molecular targets, to evaluate other relevant biologic effects and to determine clinically relevant outcomes/correlates. Major emphasis shall be on Phase II studies, pilot protocols that explore promising combination therapies, and high priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting.

Therapeutic Modulation of Angiogenesis in Disease

The purpose of this initiative, cosponsored by the NCI, NHLBI, and NEI; is to encourage the translation of basic knowledge of the angiogenic process into therapeutic applications. It may also promote new collaborations between basic and clinical scientists currently engaged in this area of research to design novel therapeutic approaches to disease.

Clinical Trials Restructuring

NCI and many of the clinical researchers it supports are re-engineering the Institute's clinical trials program. The aim is to enrich the scientific input in clinical trials conception and design, streamline operations, and broaden access to participation in trials by both patients and physicians across the country. Pilot studies are planned that will test new systems for realizing these goals. Breast cancer is one of the diseases targeted for inclusion in the Cancer Trials Support Units. The CTSU will serve as a "one-stop shop" to allow user access to NCI-supported clinical trials by physicians and patients. Uniform informatics will be developed to allow investigators in any Cooperative Group to participate in all breast cancer trials opened in the CTSU.

Informatics and Clinical Trials

In collaboration with experts in its clinical trials program, in the cancer centers, and in industry, NCI is developing a national Cancer Informatics Infrastructure to enable the linkage, transfer, and analysis of biomedical information relating to cancer. The initial emphasis of this project is on systems to support clinical trials.

Drug Discovery and Development

Interdisciplinary Research Teams for Molecular Target Assessment

The purpose of this initiative is to discover, develop and validate the research tools that will make mechanism assessment in clinical trials and preclinical cancer models a reality. This initiative's major objective is the development of methods to assess the effects of interventions directed at specific molecular targets that produce the cancer phenotype or are associated with it.

We seek molecular assays, molecular and cellular imaging probes, and other tools that provide information on the extent to which molecular targets are affected in vivo by interventions in preclinical models and in proof-of-principle early clinical trials. Investigators are invited to form Interdisciplinary Research Teams which should include investigators with expertise in critical biological processes that encompass high-priority targets for cancer treatment or prevention; in chemistry; in molecular and cellular imaging science and technology; in invasive and/or non-invasive evaluation of the molecular effects of drugs; in preclinical models; and in early clinical trials. The intent is to develop research tools that will, directly and indirectly, revolutionize all stages of research relating to the development of drugs to treat or prevent cancer. Application Receipt Date: March 15, 2000

Rapid Access to Intervention Development (RAID)

This is a competitive program that places NCI's drug development resources at the service of academic discovery laboratories. Investigators who have molecules that hold promise for cancer treatment but who lack access to the resources required to develop these molecules to the point that they are ready for clinical trials are invited to submit proposals twice a year. Those selected for support are granted assistance with any necessary preclinical development steps which will enable IND filing and the initiation of proof-of principle clinical trials.

Non-Mammalian Organisms as Models for Anti-Cancer Drug Discovery

This Program Announcement (PA) encourages the use of non-mammalian organisms to discover new cancer therapies. The goal is to identify key genes, enzymatic activities, components of signaling pathways, or cellular processes, that are altered in human cancer as potential intervention points or targets that could be used in the design of new cancer drugs. Projects could focus on validating inferences already drawn from comparative study of cancerous and normal cells, exploring promising leads from the nature of mutations known to be associated with cancer development, or testing hypotheses generated by the identification of new and unknown gene products, such as those sequenced through the NCI's Cancer Genome Anatomy Project (CGAP). For example, projects may include development of organisms in which genes in key pathways or processes are mutated or in which human transgenes are expressed to simulate changes known to occur in human cancers. These genetic manipulations could present a "proof of principle" or validation of the importance of the target genes to the development of cancer. Some examples of genes that are well studied in model organisms and known or strongly suspected of involvement in cancer include oncogenes, proto-oncogenes, some cell cycle and signal transduction genes, and DNA repair genes.

The use of multiple grant funding mechanisms allows support for a broad range of projects at various stages of development. The exploratory/developmental R21 mechanism supports pilot projects or feasibility studies for new or underdeveloped approaches. Accordingly, a sound research plan, with only preliminary data, are sufficient. The R01 supports more advanced projects and also collaborative research efforts between experts in non-mammalian biology and investigators with experience in mammalian cancer models for comparative or proof of principle, validation studies. A second PA has also been issued inviting applications for SBIR/STTR proposals.

Specimen Resources

Successful development of molecular diagnostics depends on availability of tumor tissue specimens. The NCI maintains a Human Specimen and Data Information System website (http://www.specimens.ims.nci.nih.gov). Other Human Tissue Resources for cancer research may be available through collaborative arrangements. NCI's Tissue Expediter facilitates these collaborative interactions. Additional information on breast cancer tissue resources can be found on the NCI-Breast Cancer Specimen and Data Information System (http://www-napbc.ims.nci.nih.gov).

Other NCI programs and initiatives related to human specimens include:

The NCI Cooperative Human Tissue Network (CHTN).

This network provides normal, benign, pre-cancerous and cancerous human tissue to the scientific community for basic and developmental studies in many areas of cancer research. See the CHTN web site (http://www-chtn.ims.nci.nih.gov) for further information.

The NCI Cooperative Breast Cancer Tissue Resource (CBCTR).

This resource can provide researchers with access to approximately 9,000 cases of formalin-fixed, paraffin-embedded primary breast cancer tissue samples, with associated pathology and clinical data. The collection is particularly well-suited for validation studies of diagnostic and prognostic markers. The CBCTR's web site (http://www cbctr.ims.nci.nih.gov) provides more information. The NCI Clinical Trials Cooperative Groups have banked tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. These banked specimens are most useful for clinical correlative studies on uniformly treated patient populations.

Correlative Studies Using Specimens from Treatment Trials

NCI is currently soliciting research grant applications to promote collaborations and interactions between basic researchers and clinical investigators to advance research on clinical correlations that can improve therapeutic approaches. In many instances, the laboratory investigators are already recipients of R01 or P01 support for their basic research. These laboratory investigators may not have access to patient specimens for pilot or large scale evaluation of new diagnostic or prognostic markers. The Clinical Trials Cooperative Group mechanism (U10) provides support for patient accrual, tumor and specimen banks for specific diseases, and reference labs necessary for the diagnosis and monitoring of patients. The new initiatives propose to link these peer-approved activities and provide a mechanism to obtain definitive data on the relationship of biological features and the clinical behavior of the tumors. The Program Announcements solicit grant applications to support correlative prognostic marker studies using specimens from single institution trials or large multi institutional (e.g., NCI Clinical Trials Cooperative Group) clinical trials.

Models

Animal Models

NCI is funding the establishment of a consortium to develop and validate mouse models for human cancer. The existence of models that truly reflect the behavior of human cancer and its responsiveness to preventive and therapeutic maneuvers would have a profound effect on our ability to understand the process of malignant transformation and to develop interventions to prevent or treat it. NCI also plans to annually issue a call for grant supplements from investigators interested in developing mouse models for human cancer as an extension of the approved content of their grant. Additional supplements for model systems other than the mouse are considered on an individual basis. Note: The receipt date for the RFA below has passed. It is provided for resource information only.

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The use of multiple grant funding mechanisms allows support for a broad range of projects at various stages of development. The exploratory/developmental R21 mechanism supports pilot projects or feasibility studies for new or underdeveloped approaches. Accordingly, a sound research plan, with only preliminary data, are sufficient. The R01 supports more advanced projects and also collaborative research efforts between experts in non-mammalian biology and investigators with experience in mammalian cancer models for comparative or proof of principle, validation studies. A second PA has also been issued inviting applications for SBIR/STTR proposals.

Item

Prostate Cancer -- Prostate cancer is the single most common form of cancer in men in the United States. An estimated 179,000 men will be diagnosed with prostate cancer and 37,000 men will die from prostate cancer in 1999. The Committee urges the NCI and other institutes to

aggressively increase efforts that will lead to the development of new treatments, new preventives, and new interventions with the potential to improve or extend the lives of men touched by prostate cancer. (p. 112)

Action taken or to be taken

Please refer to pages NCI - 121 through NCI - 129 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

[Prostate Cancer effecting different ethnic populations] -- The incidence and severity of prostate cancer varies in different ethnic populations. African-American men are more than twice as likely to die of prostate cancer than Caucasian men. In African-American men, prostate cancer is also generally more advanced at the time of diagnosis. Chinese men living in China have incidence and mortality rates that are 3-10 times lower than U.S. men. Reasons for the large racial difference in risk are currently unclear. The Committee urges NCI to conduct studies to identify risk factors for prostate cancer in several populations, including African Americans and Chinese. The Committee also encourages NCI to study the associations of dietary patterns with prostate cancer, and variations in the role of diet in different racial and ethnic groups. (p. 112)

Action taken or to be taken

Please refer to pages NCI – 121 through NCI - 129 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- Increased use of serum analysis for prostate-specific antigen (PSA), the primary method of screening for prostate cancer, has led to an increased detection rate for prostate cancer. However, only 30 percent of early stage disease will progress to clinically relevant disease within the lifetime of the patient. The Committee encourages NCI to develop methods to identify those patients at risk of progression who would benefit from aggressive therapy while sparing low-risk patients the morbidity resulting from aggressive treatment of slow-growing disease. The Committee also encourages NCI to carry out clinical trials that will determine whether yearly screening for prostate cancer using the PSA blood test will decrease mortality from prostate cancer. (p. 112)

Action taken or to be taken

Please refer to pages NCI - 121 through NCI – 129 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- The NCI has identified a need to restructure the clinical trials program to make it faster, more flexible, more easily accessible to patients, and more responsive to key therapeutic questions. The Committee encourages NCI to test new systems that will identify the best trials, improve trial planning, speed trial activation, and improve availability of trials to patients. The Committee encourages NCI to implement programs to assist investigators in academia and in small businesses in getting compounds with promise for treatment and prevention of prostate cancer into clinical testing using NCI's existing development resources. Several key treatment questions need to be addressed. The Committee urges NCI to initiate clinical trials that will optimize hormonal and chemotherapeutic approaches for the most common clinical presentations of prostate cancer. (p. 112)

Action taken or to be taken

Please refer to pages NCI - 121 through NCI – 129 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- The Committee is encouraged by NCI's collaborations with the Department of Defense in fighting this devastating disease, and urges NCI to continue to strengthen and expand its prostate cancer research portfolio. The Committee further expects the NCI to accelerate spending on prostate cancer, and consult closely with the research community, clinicians and patient groups to identify promising new avenues of basic and clinical research. (p. 112-113)

Action taken or to be taken

Please refer to pages NCI - 121 through NCI - 129 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Lymphoma **--** Lymphoma currently has one of the highest incidence rates among all cancers in the U.S. It is estimated that approximately 64,000 Americans will be diagnosed with lymphoid cancer in 1999. While progress is being made in the treatment of many kinds of cancer, incidences of non-Hodgkin's lymphoma have nearly doubled since the early 1980s. The Committee encourages NCI to increase lymphoma research to promote new innovative research models based upon collaborative methods that maximize the results of ongoing lymphoma research at the NCI. The Committee also encourages NCI to collaborate with their counterparts at the NIEHS in exploring environmental factors that may contribute to the development of the disease. The Committee also recommends that NCI coordinate its research efforts with the CDC, and encourages NCI to consider exploratory research on incurable lymphomas such as log-grade and aggressive incurable lymphomas. (p. 113)

Action taken or to be taken

Please refer to pages NCI - 91 through NCI - 100 of this document for NCI's response to this significant item regarding Lymphoma.

Item

Cancer coordination -- The Committee encourages NCI to continue its leadership role as coordinator of the National Cancer Program. As the facilitator of the nation's fight against cancer, the Committee specifically encourages NCI to continue to work in collaboration with private/voluntary sector organizations, the CDC, and other federal agencies to address the coordination challenges outlined in the National Cancer Advisory Board's report entitled, 'Cancer at a Crossroads.' (p. 113)

Action taken or to be taken

Please refer to pages NCI - 40 through NCI - 52 of this document for NCI's response to this significant item regarding Cancer Coordination.

Item

Cancer in minority populations -- The Committee remains concerned over recent statistics citing higher incidences of cancer among the native Hawaiian population. In comparison to other ethnic and racial groups, native Hawaiians have the highest incidence of the most common forms of cancer such as breast, colon, and lung cancer. The Committee encourages continued research in the areas of prevention and detection, utilizing nurse practitioners in community-based centers for screening and education for the underserved populations. (p. 113)

Action taken or to be taken

Data on the increased burden of cancer in the native Hawaiian population comes primarily from the NCI Surveillance, Epidemiology, and End Results (SEER) Program. SEER is a rich source of data on racial/ethnic differences in cancer incidence and mortality in the U.S. This program, begun in 1973, collects stage-at-diagnosis, age, race, gender, initial treatment, and other pertinent data on all people diagnosed with cancer in ten defined geographic regions of the U.S. SEER also collects mortality data and can perform lifetime follow-up on each cancer patient. The geographic areas comprising SEER represent approximately 14 percent of the entire U.S. population. Certain minority groups are over sampled in its geographic distribution, which is useful since many of these population subgroups are small in absolute number in the U.S. Currently, 25 percent of the American Hispanic population, 41 percent of the Asian/Pacific Islander population (43 percent of all Chinese Americans and 60 percent of all Japanese Americans), 27 percent of American Indian and Alaska Native populations, and 12 percent of the African-American population and virtually all native Hawaiians reside in the SEER areas.

Native Hawaiians have the second highest all-cancer mortality and lung cancer mortality rates (African-American males and Alaska Native females have the highest rates, respectively). Liver and stomach cancer mortality rates for Hawaiian males are greater than for white males.

Hawaiian women have the second highest breast cancer mortality rate (next to African-American females), and their stomach cancer mortality rate is 374 percent greater than the white female rate. Much of the increased cancer risk among Native Hawaiians appears to be due to known behavioral or lifestyle risk factors such as smoking, alcohol consumption, and obesity. A recent study found that 64 percent of Native Hawaiians are overweight compared to other ethnicities in the state.

Many aspects of the cancer problems of native Hawaiians do not appear to be unique, and NCI believes all things learned about cancer biology, prevention and control have benefit to native Hawaiians. The projects listed below are from NCI's research portfolio and specifically involve a number of native Hawaiians.

Genetic Susceptibility to Cancer in Multiethnic Cohorts. Collaborating investigators at the University of Hawaii at Manoa and the University of Southern California Medical School have established a substantial cohort comprised of minority populations (African-Americans, Hispanic, Japanese and Native Hawaiians) and whites. The cohort of 202,136 individuals has been characterized by questionnaires regarding detailed dietary histories, past medical histories and other lifestyle characteristics, and is being followed for all incident cancer cases utilizing population-based cancer registries in each location. This cohort is of sufficient size and heterogeneity to study the relationship between environmental risk factors, as determined primarily by the questionnaire, and genes that may be important alone or as sources of potential interaction in determining the risk of sporadic cancers of the colorectum, prostate, and breast.

Hawaii Family Registry of Colon Cancer. This study builds on several NIH-supported, population-based research projects on environmental and genetic factors and attitudes toward genetic testing for colorectal cancer (CRC). The aims of this application are: 1) to establish a family registry and bio-repository for high-risk families in Hawaii and to contribute data and specimens for about 130 new intermediate and high risk families for CRC (an additional 140 families from the current family study will also be contributed after publication of results); 2) to develop and pilot test protocols using the Cooperative Family Registry: a) to describe the mutational spectra and clinical characteristics of known hereditary syndromes of CRC in ethnic populations, b) to assess the penetrance of relevant mutations in individuals of various ethnic backgrounds, c) to conduct intervention studies among high risk individuals with regard to early detection, diet and exercise, d) to study psychological issues related to high familial risk and predictive genetic testing.

The Association of Diet and Other Factors with Gastric Cancer. Gastric cancer is still the second leading cause of cancer deaths in the world, although rates have declined significantly in the United States. The primary objective of this 5-year population-based, case-control study is to test the hypothesis that a variety of risk factors may be involved. A total of 436 cases and 436 controls are expected to be interviewed with collection of a blood sample during the study period. One population-based control will be frequency-matched to each case by sex, age (within 5 years) and ethnicity (Caucasian, Chinese, Filipino, Hawaiian/part-Hawaiian or Japanese). A comprehensive dietary questionnaire with about 250 food items will be administered to each study participant. This investigation will contribute to our understanding of

the role of dietary factors, H. pylori infection and family history in the etiology of gastric cancer. The findings should provide useful information towards the primary prevention of this disease.

The Minority Based Community Clinical Oncology Program funds hospitals and physicians who care for a large number of ethnic minority patients to participate in NCI funded clinical research activities. The University of Hawaii has been funded to participate in this program since 1983. As of December 1999, the NCI PDQ data base (http://cancernet.nci.nih.gov/) lists 115 NCI sponsored cancer treatment, prevention and diagnostic trials open and accruing human subjects in the state of Hawaii.

The NCI-sponsored Native Hawaiian and American Samoan Cancer Control Research Network focused on the unique cancer needs of these populations and encompassed a variety of collaborative efforts with Papa ola Lokahi (Native Hawaiian Board of Health established by the Native Hawaiian Health Care Act of 1988), the Office of Hawaiian Affairs, the Cancer Center of Hawaii, Native Hawaiian health organizations, traditional healers, scientific and lay community leaders, and civic leaders.

The Institute recently competed a request for applications for the Special Populations Network for Cancer Awareness Research and Training. These grants will fund robust and sustainable infrastructures to promote cancer awareness and education within minority and medically underserved populations. This program will follow up on the National Leadership Initiatives on Cancer, in the Hispanic, African Americans, and Appalachian communities over the past several years. It is hoped that the new initiative will appeal to additional minority populations and stimulate research in minority and underserved populations at a community level. Funded community organizations must collaborate with established researchers to define the scientific questions most pertinent to the community and the projects that will address these questions. Funded projects will become active in early 2000. This request for applications was issued in early 1999. There were an astonishing number of applications and after initial review it is anticipated that one of these networks will be based in Honolulu and will serve native Hawaiians as well as other residents of the islands.

Reaching the public with information about cancer in ways that are most likely to help people take action is a monumental task—one that no single organization can accomplish on its own. The Cancer Information Service (CIS) is a program of the NCI. Created in 1976, the CIS is the source for the latest, most accurate cancer information for patients, their families, the general public, and health professionals. Through its toll-free phone service (1-800-4-CANCER), specially trained professional staff explain scientific information in understandable terms, answer calls in English, Spanish, and from the hearing impaired. CIS information specialists provide thorough, personalized attention to each caller and answer questions about prevention, screening and early detection, diagnosis, treatment and research. All calls are confidential.

The CIS serves the United States and Puerto Rico through 14 regional offices located at cancer centers and health care institutions across the country. The CIS for the Pacific Region, sponsored by the Fred Hutchinson Cancer Research Center, serves Alaska, Hawaii, Idaho, Nevada, Oregon and Washington. The Cancer Information Service expands its reach and achieves greater impact by developing partnerships with nonprofit, private, and other

government agencies at the national, regional, and state levels. The CIS specifically reaches out to partners that have an established presence in the region, are trusted within their communities, and are dedicated to serving minority and underserved populations.

Two-thirds of Cancer Information Service partners focus on reaching minority audiences including African Americans, Hispanics, American Indians, Asian Americans, Native Hawaiians, and Alaskan Natives. More than three-quarters of Cancer Information Service partners strive to reach medically underserved audiences—(including older Americans and individuals living in communities lacking adequate health services or experiencing language, educational, financial, or transportation barriers).

The CIS provides up-to-date scientific information in lay language, assists organizations in developing education efforts to reach people who do not have easy access to cancer information and services, and studies ways to promote healthy behaviors and communicate cancer information effectively. Each year, the CIS responds to 500,000 calls and assists 4,500 organizations nationwide with cancer education efforts. The Cancer Information Service assists organizations by providing:

- Education about the latest, most accurate cancer information, resources available from NCI, and referrals
- Training on methods to educate their constituents on cancer-related topics
- Assistance in planning cancer education programs and evaluating their success
- Assistance in developing new coalitions or strengthening existing coalitions
- Advice about strategies to reach special populations

The CIS Partnership Program brings cancer information to organizations that reach people who traditionally do not seek health information. Partnership activities include a nationally coordinated, regionally focused program committed to reaching minority and underserved populations that do not have adequate access to health information and services. The CIS Partnership Program staff provide cancer information and program development assistance to organizations that reach people in particular need of cancer information and services, such as minority and medically underserved audiences. Partnership Program staff link organizations with similar goals and help them plan programs, use appropriate NCI materials, and coordinate media activities. The CIS also plays an important role in research by studying ways to promote healthy behaviors and communicate cancer information effectively.

Strengthened by its regional structure, the Cancer Information Service focuses on the distinct needs in each community to provide a service tailored to culturally diverse populations throughout the nation. The CIS Partnership Program develops partnerships with nonprofit, private, and government agencies at the national, regional, and state levels. Specifically, the CIS reaches out to partners that have an established presence in the region, are trusted within their communities, and are dedicated to serving minority and underserved populations. CIS partnerships with Native Hawaiian groups include the Worksite Breast Cancer Education Network, the Kamahameha Schools Bernice Pauhahi Bishop Estate, and the Hawaii State Department of Health.

In 2000, the CIS will work with its Hawaiian partners to increase knowledge in these areas:

- Breast and Cervical Cancer Education: Includes education about prevention, early detection, and treatment of breast and cervical cancer.
- Clinical Trials Education: Involves raising awareness of the importance of clinical trials and promoting participation.
- Tobacco Control Education: Focuses on promoting the telephone service's counseling on how to quit smoking and supporting state tobacco control efforts.
- General Cancer Awareness of Special Populations: Involves general education about prevention, detection, and treatment of cancer to diverse communities and medically underserved populations.

In addition, CIS staff may serve as a resource for their partners on a variety of other cancer-related issues important in their own regions. CIS staff may provide assistance in areas such as skin cancer education, cancer pain, and cancer survivorship. Partnership Program staff provide an array of services to meet the distinct needs of each organization, offering expertise in areas such as program planning, and coalition building. Support ranges from fulfilling a single request to serving as a long-term partner—assisting with multiple activities over a number of years.

Drawing upon the values and traditions of the Native Hawaiian culture, Cancer Information Service staff trained leaders in the Native Hawaiian community to convey the importance of screening for breast and cervical cancers to Kokua groups—women interested in learning how to improve health. To further reach Native Hawaiian women in culturally appropriate ways with these messages, the Cancer Information Service developed a Speaker's Kit, "Breast Care for Hawaii's Women," which is used by Native Hawaiian health and human service agencies, work sites, hospitals, and other organizations.

Item

Behavioral science research -- The Committee commends NCI for expanding its infrastructure to fund behavioral and population research in cancer prevention, treatment, and control. NCI is encouraged to expand its investigation of the effective provision of mental health services to improve the course of cancer treatment and to aid in the adjustment to cancer survivorship. NCI is also encouraged to build upon its collaborations with the National Institute on Drug Abuse to more thoroughly investigate issues of youth tobacco use. In particular, the Committee is interested in expanding health promotion research focused on children and youth, and interdisciplinary research on tobacco addiction and cessation. The Committee also encourages NCI to expand its research on adherence to treatment regimens and to health-promoting behaviors such as physical activity and healthy diet. (p. 114)

Action taken or to be taken

The Behavioral Research Program within the NCI was initiated October 1, 1998. As one of four programs within the Division of Cancer Control and Population Sciences (DCCPS), much has been accomplished, but much remains to be done. Given the role that health behavior plays in

the development and progression of many types of cancer, the NCI has continued to support a wide variety of health behavior research efforts. Science in the areas of tobacco control, diet and nutrition, cancer communication, and basic biobehavioral research across the health behavior spectrum has continued to be emphasized. Indeed, two of these areas, tobacco and cancer communication have been designated as "extraordinary opportunities" by the NCI, noting the importance of these areas for advancements in cancer control.

As the Committee indicated, tobacco use research is indeed one of our highest priority areas. Under the guidance of the Tobacco Control Research Branch within NCI's Division of Cancer Control and Population Sciences (DCCPS), several major initiatives in tobacco control were begun in the past year. Final analyses of the American Stop Smoking Intervention Study (ASSIST), a 17 –state effort to support and evaluate programs to prevent and control tobacco use, conducted in collaboration with the American Cancer Society, are nearing completion. As of October 1, NCI jointly funded with NIDA seven Transdisciplinary Tobacco Use Research Centers. Among other questions related to tobacco use, these centers are focusing on questions related to youth and tobacco, why people become addicted (with new insights likely to be provided by genetic research), and why certain minority groups may be especially vulnerable. Some centers are addressing problems of relapse and developing better treatments to help people quit smoking. Critically important, these Centers will also provide training for the next generation of scientists investigating health behavior and cancer. This partnership with NIDA has been extremely rewarding to date, and NCI certainly intends to expand our collaborations, starting with some supplements that will be offered to the tobacco centers to encourage research in high priority areas. A partnership with the Robert Wood Johnson Foundation will fund research aimed at determining how NCI can disseminate the best practices that are identified through the Centers' research. Finally, the Research in State and Community Tobacco Control Interventions initiative has begun, assessing the impact of a variety of tobacco control interventions, including public health policies and mass media campaigns that may impact on tobacco use at the state and community levels.

NCI's Health Communications and Informatics Research Branch (HCIRB), focusing on the "extraordinary opportunity" of cancer communication, has hired a Branch Chief with an expertise in health communication. The Branch has already collaborated with the Agency for Health Care Policy and Research (AHCPR) on the interagency agreement between NCI and the AHCPR concerning "Making Quality Count for Consumers and Patients," in support of the HHS "Quality Improvement Initiative". There has also been collaboration with the American Cancer Society in their Breast Cancer Risk Communication Workshop, with the goal of establishing standards for future risk communication initiatives concerning breast cancer. This collaboration has been strengthened by the recent national conference sponsored by the NCI on cancer risk communication, the results of which have been recently published (Journal of the National Cancer Institute). Finally, the HCIRB collaborated with MIT's media lab in sponsoring and presenting the Future of Health Technology Summit (September 1999).

NCI also intends to encourage more research on health promotion in children and youth. One of the priorities of the Health Promotion Research Branch is research on these target groups. Research at all levels is needed to learn how to motivate healthy practices among children and youth. This will require basic as well as applied research. In addition, DCCPS will complete by

late summer a series of reviews intended to help us define next steps in the research agenda on diet, weight and physical activity. An in-house group has been reviewing the epidemiological evidence in these areas and making recommendations. NCI also has a contract with the AHCPR to obtain a synthesis of the research evidence on the effectiveness of behavioral interventions for dietary change. There is also an evaluation group which will make recommendations about future directions for the 5-A-Day Program. These efforts should enable us to formulate the future directions for health promotion research at the NCI. Issues of diet and physical activity are especially important for cancer survivors. A number of NCI epidemiologists are conducting research aimed at elucidating the relationships between exercise and diet and cancer incidence and progression as well as how these behaviors may improve quality of life of people who have or have had cancer.

The Basic Biobehavioral Research Branch sponsored a Request for Applications in the area of cancer control, and funded a number of studies investigating the role of genetics in tobacco control, focusing on factors interacting with genetics to better predict smoking initiation and cessation. This research will also help to provide more informed intervention studies.

With the creation in 1996 of the Office of Cancer Survivorship (OCS), the NCI has acknowledged the need for more information about this growing population of cancer survivors and their unique concerns. It is currently estimated that there are over 8 million survivors of childhood or adult cancer in the United States alone. Despite this large figure, relatively little is known about the demographic characteristics of this population, their current health or their unique needs. Historically, the majority of the behavioral research supported by NCI and conducted among cancer patients has focused on describing or addressing the physical, psychological and social impact of cancer in those newly diagnosed or in active treatment. Few studies have included samples of patients who were evaluated or followed more than one to two years after their cancer treatment. Fewer still have looked at those alive more than 5 years after diagnosis. Survivors themselves report multiple challenges secondary to their illness: persistent problems with fatigue, altered body image, questions about fertility and sexuality, fear of recurrence, worry about second cancers, employment and insurance discrimination due to their cancer history.

The OCS has supported two research initiatives designed to expand our knowledge about the medical, psychosocial and economic outcomes of groups of cancer survivors, and the health of long-term survivors (more than five years since diagnosis) in particular. A total of 35 projects were funded under these mechanisms. Important in this process has been encouragement to researchers to examine the full range of survivors' issues. While many of the grants are studying the potential physiologic and medical late effects of treatment, 18, or more than half (51%), specifically examine the mental health impact of cancer diagnosis and treatment; 4 of these (22%) will test interventions to improve patient adjustment to illness. Most recently (10/99), the OCS became responsible for a new Mind/Body Center grant at the University of Miami that will promote psycho-oncology research across the illness and recovery continuum. This application was the result of a trans NIH collaboration, in response to a congressional mandate that included a funding set aside, to establish centers for the Study of Mind Body Interactions and Health. The establishment of this center, responding as it does to the public's growing interest in and use of complementary approaches in cancer care, represents a promising new area of research. All four

of the projects proposed under the umbrella of the center include interventions that aim to improve the health behaviors (e.g., stress management) and/or quality of life of cancer survivors.

The OCS also has sponsored two workshops, bringing together experts in the field of medical and psychosocial aspects of cancer to help educate researchers, clinicians and consumers about the impact of cancer on patients and families after treatment ends, and to stimulate new research in the area of cancer survivorship. Over the last year, starting in October 1998, a working group on diet, weight and physical activity was created and included members from across the Division of Cancer Control and Population Sciences (DCCPS). The mandate of the group is to review the state of the science in these areas, identify gaps in our knowledge base, and ultimately, to develop recommendations to address research needs and priorities.

This spring, the Office recruited a new, full-time Director with experience in working with both the research and consumer advocacy communities in the field of psycho-oncology. The OCS has moved to double its staff commensurate with its increased role in grant funding, education and outreach in the area of cancer survivorship.

Current Activities and Future Plans

The Tobacco Control Research Branch will be heavily involved in implementing the "extraordinary opportunity" for investment in tobacco-related research. In addition, this Branch will oversee the progress of research projects supported by the initiatives noted above. The staff of the Health Communications and Informatics Research Branch are currently working with the Cancer Information Service Research Consortium to discuss research programs to enhance the effectiveness of Cancer Information Service activities in disseminating health information and meeting public cancer information needs. A initiative to create Centers of Excellence in Cancer Communications Research is being finalized. This program plans to identify and fund 6-8 research centers for transdisciplinary cancer communications research to promote development of new health communication technologies, programs, message strategies, and interventions to reduce the cancer burden throughout the nation and to promote public health. In addition, the HCIRB staff will continue to work to further support the "extraordinary opportunity" in cancer communication.

In the area of health behaviors/nutrition, plans are underway to host a second Nutrition and Behavior Research Grantees Meeting, including plans to expand the participating members to other organizations interested in nutrition and behavior research. Finally, in the area of basic biobehavioral research, a second request for applications has been issued, with applications due at the beginning of fiscal year 2000. This request includes applications devoted to tobacco use, but expands the focus to genetic testing, the effect of psychological variables on morbidity and progression of disease, and other non-tobacco related research areas. NCI continues to need basic biobehavioral research, which helps to inform our interventions by noting which biological mechanisms may be involved in successful and unsuccessful intervention attempts.

The Office of Cancer Survivorship staff are currently working with members of the Surveillance and Applied Research Programs within the DCCPS to gather information from the SEER databases that can be used to better describe the sociodemographic and medical characteristics of

cancer survivors treated nationally. This information will be particularly useful in broadening our understanding of who are today's survivors and what this population may look like in the next millennium. Importantly, it will also be useful in identifying groups of people with a cancer history (e.g., minority patients, rural inhabitants, those treated for colon or lung cancer) who may be under-represented among our survivors, and for whom intervention initiatives to reduce the disproportionate burden of death or disability due to cancer illness or treatment should be targeted. The SEER collaboration will also provide a first attempt to determine if this valuable database and mechanism can be used in the future to monitor more specific survivorship outcomes (i.e., beyond mortality, to incorporate such aspects as psychosocial well-being, work status, family situation, etc.). At the same time, the OCS staff are working with members of the Applied Sociocultural Research Branch within DCCPS to review the existing literature on minority cancer survivors and inform us of where the gaps in our knowledge, and hence research, currently exist.

OCS staff also are serving as consultants to the Office of Cancer Information, Communication and Education on an update of their publication *Facing Forward* which serves as a guide to issues and resources for survivors and their families. Within the next month (11/99), the OCS expects to launch its new web site. This user-friendly site will serve as a resource for researchers and practitioners, as well as survivors and their families. Included will be information on what is new in cancer survivorship, opportunities for funding and training in this area, and for consumers, how to become involved in the research direction and oversight process. Both of these last two efforts will contribute to the new emphasis on cancer communication occurring institute-wide.

As the population of cancer survivors continues to grow, an important challenge will be to describe and address the special needs of these individuals and their families to reduce the burden of cancer for all. To achieve this, the OCS will encourage efforts within the research community to develop new measurement tools and novel assessment strategies that will allow us to monitor the health-related quality of life of survivors across the disease and recovery continuum. The OCS will also promote, through sponsored research and workshops, closer examination of the efficacy of psychosocial, medical or behavioral interventions in reducing the physical, emotional and social morbidity or economic costs associated with survival, and in promoting improved health outcomes for those diagnosed and treated for cancer. With the aging of the population, it is expected that the number of individuals being diagnosed with, and, importantly, surviving for long periods following, cancer will increase. At the same time, the delivery of cancer treatments will likely continue to move into the outpatient setting, with more care being delivered at home or by loved ones. The OCS recognizes this growing demand on the family and expects that future research initiatives will need to be developed that examine more closely the cost to family providers, with respect to their functioning and health, of such extended care. The location of the OCS within the Division of Cancer Control and Population Sciences, with its growing resources in the area of outcomes, bio-behavioral and population science research, provides a rich collaborative setting within which to advance our understanding and care of cancer survivors.

Training

The NCI has expanded substantially opportunities for training for behavioral scientists with cancer-related interests. By supporting a broader range of training and career award mechanisms, the NCI now provides behavioral scientists with funding opportunities throughout their careers. An important step in addressing early pre-doctoral and postdoctoral training in behavioral science has been the issuance of NCI's new R25 Cancer Education and Career Development Program. This program supports the development of interdisciplinary training programs that provide behavioral scientists with the necessary knowledge and skills to conduct cancer-related research. In addition, the NCI supports the newly revised K23 Mentored Research Career Development award, which is open to clinical psychologists and other clinically oriented behavioral scientists. This award provides clinicians with the opportunity to improve their research skills and experiences in order to increase their competitiveness as investigators and applicants for research grants. This mechanism is complemented by the NCI's K07 Career Development Award in Cancer Prevention, Control, and Population Sciences. Although this program has been open to behavioral scientist applicants in the past, it was recently revised to specifically highlight behavioral science and is now being marketed directly to behavioral scientists through advertisements in relevant publications. Behavioral scientists who have completed their doctoral training and mentored experience are eligible for the new NCI K22 Transition Award, which provides support to investigators who are moving from a mentored to an independent research position. This award is expected to increase opportunities for behavioral scientists who are seeking faculty positions at our nation's leading cancer research institutions. These award mechanisms will not achieve their potential unless they are promoted actively by staff within the NCI. We are using a variety of strategies to promote these mechanisms. For example, our staff speak to many national and local meetings, and provide consultation to interested applicants by phone and in person. An additional source of behavioral science training is offered through SPORE grants. Particularly noteworthy is the training component of our recently funded Transdisciplinary Tobacco Use Research Centers. It is expected that these Centers will train the next generation of behavioral scientists (and others) who will conduct research on tobacco use.

Item

Hepatitis C Consensus Development Conference -- The Committee is aware that several of the significant new research recommendations of the NIH-sponsored Hepatitis C (HCV) Consensus Development Conference impacts directly on the research portfolio of the NCI. This research includes the NCI recommendation that studies are needed regarding the mechanism of development of hepatocellular carcinoma in patients with HCV. The Committee encourages the NCI to increase research in this area. (p. 114)

Action taken or to be taken

The hepatitis C virus (HCV) is one of six viruses (A, B, C, D, E and G) that together account for the majority of cases of viral hepatitis. According to the National Health and Nutrition Examination Survey of 1988-94 and other population-based surveys, nearly four million Americans are infected with hepatitis C. The infection is more common in minority populations

(3.2 percent of African-Americans and 2.1 percent of Mexican-Americans) than in non-Hispanic whites (1.5 percent). Approximately 30,000 acute new infections are estimated to occur each year, about 25-30 percent of which are clinically diagnosed, and HCV accounts for 20 percent of all cases of acute hepatitis. HCV is responsible for an estimated 8,000-10,000 deaths annually, and without effective intervention that number is postulated to triple in the next 10-20 years. The virus is now the leading reason for liver transplantation in the United States, and is recognized as a significant etiological agent for hepatocellular carcinoma.

The NIH consensus conference on Management of Hepatitis C held March 24-26, 1997 made a number of recommendations concerning research opportunities. Among these was that the mechanism of development of hepatocellular carcinoma in patients with hepatitis C infection needs elucidation. The consensus conference also noted the need for vaccines and new antiviral agents, and indicated that vaccine development will require a better understanding of both cellular and humoral immunity to HCV, the nature of antigenic variation of the virus, and the mechanism(s) by which HCV regularly escapes the host immune system and establishes persistent infection. The absence of suitable animal and tissue culture models of HCV infection and disease progression, including cancer, was also noted by the conference to be "a major bottleneck" and their development to be a "high priority." In recognition of the significant role of hepatitis C in the etiology of human liver diseases, including cancer, new multi-Institute Requests for Grant Applications have been issued to address many of these issues. These initiatives, and other research activities, result in part from the activities of the NIH HCV Working Group, a group consisting of representatives from several NIH Institutes and Centers, including NCI, with an interest in HCV infection and its sequelae including cirrhosis and liver cancer.

The NCI coauthored and co-funded a Request for Applications (RFA) for "Hepatitis C: Natural History, Pathogenesis, Therapy and Prevention" which supported high quality research to address many of the recommendations of the 1997 NIH Consensus Conference. Of the total of $5.15 million set aside by NIH Institutes and Centers for the first year of funding of this RFA, the NCI contributed $1.2 million in fiscal year 1999, to fund high quality applications dealing with protective immunity, immunotherapy, and vaccines for HCV, and with epidemiologic and natural history studies of human HCV infections. These grants will be funded for the full five year terms recommended by the review group.

An additional RFA, utilizing the Small Business Innovative Research mechanism was reviewed in fiscal year 1999 and will be funded in fiscal year 2000. NIAID and NCI are each contributing up to $1.5 million to this RFA, and the NCRR, NIDDK, and NIAAA have also committed funds. This targeted effort will encourage small businesses to participate in the development of small animal models for studies of pathogenic and cancer causing properties of HCV, as recommended by the Consensus Conference.

In addition to the newly funded grants mentioned above, the NCI is currently supporting traditional research grants on Hepatitis C virus. Three virology grants include studies on virus replication, host and viral factors responsible for HCV persistence and disease production, and development of possible antivirals and vaccines for HCV. An infectious disease epidemiology grant includes HCV as a part of a larger study of the epidemiology of human T-lymphotrophic

virus in Japan. Although these grants were funded prior to the 1997 NIH Consensus Conference on HCV, all of them are directly related to the research goals of understanding how HCV causes human cancer and developing vaccines to prevent the initial infection with HCV suggested by participants in the Consensus Conference.

NCI intramural scientists are utilizing molecular genetic and clinical epidemiological approaches to characterize variations in more than 25 genes that affect infection or disease progression following exposure to HCV and other viral pathogens. In addition, the rates of infection with HCV and the human immunodeficiency virus have been followed since 1982 in a cohort of more than 2000 persons with hemophilia in the Multi-center Hemophilia Cohort Study. This study demonstrated that, after AIDS, hepatic failure was a leading cause of death among persons with hemophilia.

NCI staff are active participants in the NIH HCV working group, whose function is to plan and develop an NIH-wide strategy for dealing with HCV infection and all of its sequelae, from cirrhosis through cancer. The working group has prepared a draft strategic plan for studies on etiologic mechanisms, prevention (including preventive vaccines), new diagnostic and prognostic tests, and novel therapeutic measures. It is anticipated that this draft strategic plan will be reviewed by extramural scientific experts and the NIH Institutes and Centers with an interest in HCV and/or liver cancer before being submitted to the NIH for formal approval. As a result of the two previously mentioned cooperative RFAs, NCI has substantially increased its research investment in studies of the virology and epidemiology of HCV as it relates to causative mechanism(s) of human liver cancer. The Institute will continue to support research as well as workshops or conferences to determine the scientific state of the art in HCV research. These workshops will also solicit the best professional judgement recommendations for research activities on the role of HCV in human cancer, and in the longer term, possible preventive or therapeutic approaches for decreasing or eliminating this disease from our population.

Item

Neurofibromatosis -- Research into neurofibromatosis (NF) is a priority for the Committee. Significant advances continue to be made in NF research since the discovery of the NF1 and NF2 gene, including the recent discovery that NF is involved with the c-AMP pathway affecting learning disabilities, in addition to its cancer-fighting tumor suppressor functions. NF research also has significant potential for other large patient populations since NF genes have been implicated in the signaling process that determines cell growth and cell differentiation. The Committee encourages NCI to intensify and expand its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation and clinical trials. The Committee encourages NCI to use all available mechanisms, including requests for applications, program announcements, and the national cooperative drug discovery group program. Progress in developing new technologies and enhancing the understanding of the fundamental process of cancer will also benefit specific disorders such as NF. The Committee urges NCI to continue to coordinate its efforts with NINDS and other Institutes and be prepared to report on the status of the NF research grant program at its fiscal year 2001 appropriations hearing. (p. 114)

Action taken or to be taken

Please refer to pages NCI - 105 through NCI - 110 of this document for NCI's response to this significant item regarding Neurofibromatosis.

Item

Sexually transmissible infections and cervical cancer -- Several sexually transmissible infections (STI's) such as the human papillomavirus and herpes are associated with an increased risk of cervical cancer. The Committee urges NCI to expedite new and current vaccines aimed at preventing the transmission of sexually transmissible infections and reducing their oncogenic potential. The Committee also requests that additional clinical trials be established to advance testing for STI vaccinations for women.

Action taken or to be taken

Please refer to pages NCI - 56 through NCI - 60 of this document for NCI's response to this significant item regarding Sexually transmissible infections.

Item

Ovarian and cervical cancer -- Ovarian cancer remains one of the deadliest cancers for women, in part due to the lack of effective early screening methods. According to 1998 estimates, 25,400 new cases of ovarian cancer and 14,500 deaths from ovarian cancer are expected each year. The Committee strongly urges NCI to expedite current research on screening methods to detect, diagnose, and identify staging of ovarian cancer. The Committee believes that identification of a cost-effective screening strategy could result in earlier diagnosis for women and higher cure rates. Similarly, 15,000 cases of cervical cancer are diagnosed annually, and 5,000 women die from the disease. NCI is strongly urged to accelerate research in this area. (p. 115)

Action taken or to be taken

The magnitude and trends in cancers in the United States are tracked by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. SEER data indicate that ovarian cancer is the fifth leading site of new cancer cases for women and the fifth leading cause of cancer deaths in women. Over 25,000 new cases of ovarian cancer were diagnosed in 1999 and nearly 15,000 American women were killed by ovarian cancer. An estimated 12,800 cases of invasive cervical cancer were diagnosed in America in 1999 and nearly 5,000 American women died of this disease. Although incidence and death rates have been declining, cervical cancer remains in the 10th most frequently diagnosed cancer in U.S. women, and over 200,000 American women are living having had a diagnosis of cervical cancer.

In FY 1999, expended approximately $44M on research on ovarian cancer. The NCI's research portfolio contains over 250 research projects related to ovarian cancer. To assist in prioritizing research on this disease, the NCI in December 1997 organized a strategic planning meeting in conjunction with the Society of Gynecologic Oncologists and the DHHS Office of Women's

Health. The recommendations from that meeting were published by the NCI in April, 1998. In December, 1998, the NCI, again in conjunction with the Society of Gynecologic Oncologists and the DHHS Office of Women's Health, organized a follow-up meeting to determine how best to implement the 1997 recommendations.

In accordance with the 1997 recommendations, the NCI advertised for applications to expand the current SPORE program to ovarian cancer. Ten applications were reviewed in spring, 1999. Awards, totaling $5.85 million were made to four institutions in September, 1999. These four SPOREs will be centered at the University of Texas MD Anderson Cancer Center, the Fred Hutchinson Cancer Research Center, the Fox Chase Cancer Center, and the University of Alabama at Birmingham. The projects to be funded focus on translation research on the biology, prevention, evaluation of risk, screening, and treatment.

The NCI has created a multi-institutional network to develop sensitive and specific biomarkers for the earlier detection of cancer (the Early Detection Research Network). One component of this network is a consortium of research centers which will work together to identify better markers for ovarian cancer. About $1.5 M has been awarded for biomarkers research focusing on earlier detection of ovarian cancer.

The Cancer Genome Anatomy Project (CGAP) continues to utilize the newest technologies to identify and characterize the genes of normal, precancerous and malignant ovarian tissue. Currently, nearly 1700 genes unique to ovarian tissue have been isolated from normal and cancerous tissues. All information from CGAP is available to researchers for studies leading to an understanding of the mechanisms of the development and progression of cancer. Some of these unique genes may be useful as markers for early detection, prognosis, and/or progression.

The PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial, begun in 1991 and continuing for 16 years, studies whether certain screening tests are effective in the early detection of specific cancers. For ovarian cancer, the researchers are testing whether using a blood test for the tumor marker known as CA-125 and transvaginal ultrasound will decrease the number of deaths from the disease.

The NCI has also organized a working group on ovarian cancer screening which will bring together US and international experts who will meet every six months to review new developments in imaging and markers, as well as data from the ongoing PLCO screening trial. As progress in imaging and markers is made, this working group will be able to design follow-up phase III trials as appropriate.

The NCI has organized a working group on cancer genetics for women with BRCA1 and BRCA2 mutations that increase a woman’s risk for breast and ovarian cancers. This group brings together representatives of the Cancer Family Registries and the Cancer Genetics Network with representatives of the Clinical Trials Cooperative Groups and the Society of Gynecologic Oncologists. The goal of the working group is to develop prospective cohort studies and clinical trials to help identify interventions which can reduce the risk of developing breast or ovarian cancer, help these women make decisions on reproductive issues, such as child-bearing and the

use of hormonal replacement therapy, and help delineate the contributions of environment, reproductive health, and genetics upon the risk of developing cancer.

Clinical Trials Cooperative Groups in the United States, Europe, and Australia have established the Gynecologic Cancer Intergroup (GCIG). This committee, which meets every six months, helps coordinate phase III clinical trials in ovarian and other gynecologic malignancies. Investigators from the US are working with doctors from the United Kingdom, Italy, and Denmark to plan a large, 4000-patient trial for women with ovarian cancer. As currently designed, this trial will evaluate the role of two new drugs, gemcitabine and topotecan, as well as a new formulation, liposomal doxorubicin, in the primary treatment of women with advanced ovarian cancer.

The NCI is also working with the Clinical Trials Cooperative Groups and the NCI-designated Cancer Centers to evaluate and improve quality of life among ovarian cancer patients and survivors. The Office of Cancer Survivorship, within the Division of Cancer Control and Population Science, has a particular focus on these issues.

The Director's Challenge initiative supports the application of powerful new technologies to the analysis of molecular changes in human tumors (molecular profiles). The initiative challenges the scientific community to develop new tumor classification systems based on the patterns of these molecular changes. These molecular profiles will complement the current morphology-based tumor classification systems which often are not able to distinguish patients with tumors that appear to be similar but who will have very different clinical outcomes. Knowing the molecular changes that have taken place in individual tumors may allow physicians to make more effective management decisions for patients.

Two research projects developing molecular profiles for ovarian tumors were supported in the first round of funding of the Director's Challenge initiative. Significant variation exists in the classification of ovarian tumors based on morphological features. This variation makes effective management of individual ovarian cancer patients difficult. Both research projects will develop molecular profiles that correlate with the degree of malignancy and the outcome for the patients with the most common type of ovarian tumors. These molecular profiles may allow physicians to select the most effective therapy for individual patients. In addition to the primary focus, one of the projects will develop molecular profiles that identify patients who will respond to platinum based therapies. The investigators also anticipate that, based on the molecular profiles, potential new molecular targets for therapy will be identified. The second project will attempt to identify molecular profiles that distinguish the four major categories of ovarian tumors and molecular profiles that may help identify precancerous lesions of ovarian tumors. Molecular profiles that identify precancerous lesions may be critical for developing strategies to detect ovarian cancer earlier.

At least five new applications proposing development of molecular profiles in ovarian cancer are expected to be submitted for the second round of the Director's Challenge initiative.

In FY 1999, NCI spent over $62 M on cervical cancer which represents nearly a 3-fold increase in spending since 1991, an increase that is significantly larger than the increase in the total NCI

budget. NCI currently is funding 149 research projects related to prevention, detection, and treatment of cervical cancer. Early diagnosis and more effective prevention of cervical cancer remains a very high priority for the NCI.

Human papillomavirus (HPV) infections is one of the most common sexually transmitted diseases. Over half the adults in the United States have been exposed to the HPV virus at some point in their lives. In the vast majority of men and women, infection with this virus is transient and causes no adverse sequellae. In some individuals, however, the DNA of the virus becomes integrated into cellular DNA, and these individuals are at increased risk of developing cancer. HPV has been linked with cancers of the cervix, vagina, vulva, anus and oropharynx in women, as well as cancers of the penis, anus, and oropharynx in men. In the developed world, screening for precancerous changes with Pap smears has been associated with a dramatic reduction in the risk of cervical cancer. In the developing world, however, cervical cancer remains the first or second leading cause of cancer deaths among women in many countries.

The NCI has developed a comprehensive research program in HPV-associated disease. This program includes extensive study of the biology of HPV infection, focusing on how HPV infects normal epithelial cells, as well as the role of the HPV E6 and E7 proteins in blocking normal cellular control mechanisms. In addition, epidemiologic studies are seeking to identify nutritional, environmental, and reproductive factors which may increase the risk that HPV infection will lead to cancer. Epidemiologic and biologic studies are examing why women in some racial/ ethnic groups have particularly high rates of cervical cancer. Cervical cancer, for example, is more common among Vietnamese-American women, Native Hawaiian women, and Native American women than other populations. We are also studying the role of the immune system in fighting off HPV infection. Women with Human Immunodeficiency Virus (HIV) infection, for example, are at increased risk for developing cancer when infected with HPV.

As mentioned above, screening for precancerous changes with the Pap smear has become an accepted part of cancer prevention in the developed world. The NCI currently funds research to improve the accuracy of Pap smears, to develop new screening tests for precancerous and cancer cells in the cervix, and to improve imaging of precancerous changes in the cervix as well as invasive cancers. The NCI also is funding research to improve Pap smear screening among poor women, elderly women, rural women, and women among racial/ ethnic minorities.

The NCI currently has a partnership with Health Care Financing Administration (HCFA) to develop, implement and promote a short term joint promotion campaign to increase physician awareness of the risk of cervical cancer among Medicare aged women and to reverse the perception in the medical community that cervical cancer is not a serious health concern for women in this age group. The campaign is meant to serve as an impetus for physicians to promote regular pap/pelvic examinations among women 65 and older and will work in conjunction with other ongoing information campaigns about cervical cancer. These campaigns are targeted to women ages 18 and older with a special emphasis on minority and medically underserved women. Information was distributed through minority media outlets to African American, American Indian, Asian, and Hispanic communities. Specific publications have been translated into Spanish and are currently being adapted for the Vietnamese community through a collaboration with a group in California.

The NCI ASCUS/LSIL Triage Study (ALTS) is a large clinical trial involving more than 7000 women in 4 centers accross the US. This trial is designed to determine the optimal management plan for low-grade cervical cytologic abnormalities. One purpose of the ALTS trial is to determine whether HPV testing can effectively triage women with ASCUS/LSIL (atypical squamous cells of undetermined significance/low grade squamous lesions). The results of looking at HPV testing will inform clinicians about the risk of ASCUS/LSIL in the context of HPV infection and progression to higher-grade lesions. The results of the ALTS trial also have the potential to decrease the morbidity and costs associated with screening for precancerous changes of the cervix.

The NCI is working to evaluate new vaccines for the human papillomavirus, both as prevention and treatment for cervical cancer. These efforts include clinical HPV vaccine trials representing a trans-NIH effort that also involves the NIH Office of Women's Health, the NIH Office of Minority Health and the National Institute of Allergy and Infectious Diseases. These trials include vaccines developed in the intramural research program of the NCI, as well as vaccines developed by industry and university laboratories. The first phase I and II trials are currently underway at NCI-designated Cancer Centers and Clinical Trials Cooperative Groups. The NCI sponsored a meeting in fall, 1998, to bring together researchers developing vaccines from academia and industry in the US and Europe, as well as representatives from the CDC and FDA. The long-term goal is to develop an effective vaccine against cervical cancer by preventing genital HPV infection and its associated disease.

One candidate immunoprophylactic vaccine being tested is a viruslike particle vaccine developed in the intramural research program of the NCI. In animal models, which involve animal papillomaviruses, such a vaccine has shown excellent type-specific protection against experimental challenge with a high dose of the homologous virus. We have recently completed an early phase safety and immunogenicity trial of normal American volunteers who were vaccinated with VLPs from HPV16, which is the HPV type found most frequently in cervical cancer. The vaccine induced an immune response in all 60 vaccinees and was well tolerated, with mild side effects consisting mainly of headache and mild temporary local pain at the injection site, as is commonly seen with other vaccines. If the vaccine continues to perform well in additional early phase testing in the United States, we plan to undertake a large scale prospective efficacy trial of the vaccine continues to determine if the vaccine will confer protection against genital HPV infection and the cervical abnormalities it produces. A site in Costa Rica is being considered for this trial, since cervical cancer is a significant public health problem in that country and the National Cancer Institute already has an ongoing long-term natural history study of genital HPV infection and disease there. The subjects in this trial would need to be followed for several years before the efficacy of the vaccine could be determined.

The NCI's PDQ database provides information on 166 open clinical trials for cervical cancer. Of these, some 111 are NCI-sponsored trials that include 85 Phase I trials in which novel treatment approaches for cervical cancer are being tested for safety. At the other end of the development pipeline for cervical cancer treatments are 6 NCI-sponsored Phase III trials representing new treatment approaches that are closest to entering general medical practice.

The NCI currently sponsors clinical trials, nationally and internationally, for all stages of cervical cancer. For example, early in 1999, the results of five large clinical trials (three of them sponsored by the NCI) announced findings that show women with invasive cervical cancer benefit from a combination of radiation therapy and chemotherapy.

The NCI is also working with the Clinical Trials Cooperative Groups and the NCI-designated Cancer Centers to evaluate and improve quality of life among cervical cancer patients and survivors. The Office of Cancer Survivorship, within the Division of Cancer Control and Population Science, has a particular focus on these issues.

The Office of Cancer Survivorship (OCS) is currently funding 10 different studies that will provide information about the physical, psychological, social and economic outcomes of diverse samples of adult cancer survivors. Many of these studies will include survivors of gynecologic cancer and/or provide information that will be important in identifying areas in which interventions may be needed to improve cancer survivors' health or well-being. In addition, the OCS became responsible in October 1999 for a new Mind-Body Center grant at the University of Miami that will promote psycho-oncology research across the illness and recovery continuum. This application was the result of a trans-NIH collaboration, in response to a congressional mandate that included a finding set aside, to establish centers for the Study of Mind Body Interactions and Health. One of the four projects proposed under the new center will evaluate the impact of a cognitive behavioral stress management intervention on quality of life, immune function and health outcomes for women infected with HIV and human papillomavirus at high risk for cervical cancer. Findings from this research may be helpful in elucidating not only mechanisms related to disease progression, but also potential strategies to reduce cancer risk in this population of women.

The NCI currently has a partnership with HCFA to develop, implement and promote a short term joint promotion campaign to increase physician awareness of the risk of cervical cancer among Medicare aged women and to reverse the perception in the medical community that cervical cancer is not a serious health concern for women in this age group. The campaign is meant to serve as an impetus for physicians to promote regular pap/pelvic examinations among women 65 and older and will work in conjunction with other ongoing information campaigns about cervical cancer. These campaigns are targeted to women ages 18 and older with a special emphasis on minority and medically underserved women. Information was distributed through minority media outlets to African American, American Indian, Asian, and Hispanic communities. Specific publications have been translated into Spanish and are currently being adapted for the Vietnamese community through a collaboration with a group in California.
The NCI will establish a Progress Review Group (PRG) early in FY 2001 to assist in setting priorities for HPV and cervical cancer research. Like other PRGs, the cervical cancer PRG will be composed of between 21 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research. The final product of the PRG will be a report listing research priorities and discussing the extent to which these priorities are being met. NCI will issue this report in mid FY 2002.

Item

Multiple myeloma -- The Committee encourages NCI to review its research portfolio and accelerate support for promising avenues into the causes of multiple myeloma. The Committee also encourages NCI to convene a scientific workshop to determine the state of MM research and to make recommendations to the Institute for further research. The Committee further encourages NCI to integrate epidemiological and occupational health research and data gathering activities relevant to MM to learn more about the molecular pathogenesis of the disease and its suspected agents. (p. 115)

Action taken or to be taken

Please refer to pages NCI - 101 through NCI - 104 of this document for NCI's response to this significant item regarding Multiple myeloma.

Item

Head and neck carcinoma --The Committee is aware that head and neck squamous cell carcinoma is the most common head and neck cancer. Moreover, it is understood that because of the immunologic unresponsiveness of this particular type of cancer, there is a need to study mechanisms of tumor-induced immunosuppression. The NCI is expected to increase funding for Specialized Projects of Oncology Research Excellence (SPORE) in order to study head and neck squamous cell carcinoma. (p. 115)

Action taken or to be taken

Please refer to pages NCI - 87 through NCI - 91of this document for NCI's response to this significant item regarding Head and neck carcinoma.

Item

Cancer and aging -- The Committee is concerned regarding recent projections regarding the incidence of cancer relative to the aging of our population. Based upon current incidence rates, the estimated new cases of cancer are expected to increase 29 percent and cancer deaths will increase 25 percent by 2010. The Committee recognizes that the resources provided to the Institute have enabled pursuit of some of the high priority initiatives outlined in the Bypass Budget. The Committee looks forward to hearing from the Institute at next year's hearing what steps should be considered in order to address the changing demographics of cancer in this country. (p. 115)

Action taken or to be taken

Please refer to pages NCI - 52 through NCI – 56 of this document for NCI's response to this significant item regarding Cancer and aging.

Item

DES -- The Committee continues to strongly support increased efforts to study and educate the public and health professionals about the impact of exposure to the synthetic hormone diethylstilbestrol [DES]. NCI and other Institutes, along with the Office of Women's Health have developed a plan for expanded research activities in this area. The Committee continues to expect NCI to carry out this plan either internally or through a contract with CDC and/or the Office on Women's Health. In addition, educational materials for consumers and health professionals have been developed as a result of a demonstration project funded by the Committee in previous years. The Committee in concerned with progress made with this and expects NCI to contract with CDC to undertake educational efforts targeting consumers and health professionals on a national basis. The Committee expects NCI and these other agencies to continue to consult with organizations representing individuals impacted by DES as they carry out DES research and education efforts. (p. 115)

Action taken or to be taken

Since 1976, the NCI has been involved with studies of individuals who were exposed to the synthetic estrogen, diethylstilbestrol (DES). The current DES Follow-up Study is a nationwide research study following a large group of both DES-exposed and unexposed people, in order to learn as much as possible about the health effects of exposure to DES. The study is coordinated under the guidance of the NCI. Because of the large number of people exposed to DES (an estimated 10 million Americans between 1938 and 1971), it is extremely important to find out about possible long-term effects. Beginning in 1994, over 6,900 mothers, 6,500 daughters, and 3,600 sons received questionnaires. The first phase of data collection is complete, and the data are being analyzed. The next round of questionnaires will be sent out in years 2000 and 2001. NCI intramural scientists continue to work with investigators at five centers following up established DES-exposed cohorts (i.e., mothers, daughters and sons).

The follow-up of DES-exposed mothers is aimed at assessing whether these women are at increased risk of cancers other than breast, for which their risk is increased about 30%. It is important for DES-exposed daughters to continue regular screening for cervical and vaginal abnormalities since some doctors are concerned about the risk of clear cell cancer during their menopausal years. NCI is also examining DES granddaughters since there is some concern on the part of the exposed population regarding the third generation of DES-exposed mothers. So far, all examinations of this group have been normal. A study published in the New England Journal of Medicine found no overall increased risk of infertility among DES-exposed men, although there were increased frequencies of some minor genital abnormalities. Whether these abnormalities indicate that more serious conditions may develop in the future can only be determined by more systematic follow-up. It will be important to follow these men for development of prostate cancer as they age.

In August 1998, the first systematic follow-up study involving a large group of women whose mothers were given DES during pregnancy in the 1940s and 1950s was published in the Journal of the American Medical Association. This study, conducted by a team of NCI intramural

scientists, found no increase in any type of cancer except for clear cell adenocarcinoma of the vagina and cervix in women under age 30. Among the 4,500 exposed daughters in the study who were followed from 1978 through 1992, three cases of clear cell adenocarcinoma developed. The rate for other cancers over this same period was similar for the DES-exposed women and for women not exposed to DES. Currently, DES daughters do not appear to have an excess risk for cancers other than clear cell adenocarcinoma. Although this study is not the final word, this is good news for women exposed to DES in the womb. NCI would like to see continued follow-up for some time since these women are still young (the oldest being in their 40s) and more time will allow a more thorough evaluation of cancer risks. In particular, the NCI will continue to monitor women for breast cancers in their later years, when breast cancer is more common. Other aspects of DES under investigation are the effects of DES on fertility and pregnancy outcome, and the effects on mothers who received the drugs during pregnancy. Several studies have reported a small (30 percent) greater risk for breast cancer in mothers directly exposed to DES. Cancer risk in sons exposed in uteri is also being studied. An association with testicular cancer in exposed sons is not proven.

The RFA-funded cooperative agreement, "DES and Cancer of the Vagina/Cervix–Collaborative Studies," involves re-contacting patients with clear cell adenocarcinoma (CCA) and identifying newly diagnosed cases. Clinical and epidemiologic data are being collected to assess factors related to survival and recurrence of CCA among DES-exposed (cases) and non-exposed (controls) women. Research efforts include investigating DNA microsatellite instability and DNA repair gene mutations, as well as the role of human papilloma virus (HPV) in CCA carcinogenesis. Evaluation of current data indicate that most DES-exposed women with CCAC are diagnosed in stage I of the disease and there is a 93% 5 year survival rate. Survival rates decrease with later stage diagnoses, reinforcing the importance of knowledge about the health effects of DES exposure and regular screening of DES daughters for this type of cancer. A meeting of investigators was held in December of 1996 to discuss future research direction that utilize biological specimens and laboratory-based protocols.

NCI's education and outreach efforts were launched in September 1993 with the National DES Education Program which supported grants in five geographic regions of the U.S. The purpose of this grant-supported activity was to design, implement and evaluate a program to increase health information about DES exposure, and to improve early detection, diagnosis, and treatment of several medical conditions associated with DES exposure. Marking the conclusion of the 5-year grants, scientists involved in the projects met in June 1998 at the National DES Education Program meeting at NIH to present and summarize their achievements. Among them were 7 different educational booklets printed for distribution, information from which is also available on the NCI website at: http://dccps.nci.nih.gov/ASRB/pubs/DES_Pubs/directory.html and from *DES Action*. A reference document for physicians is also completed and is ready for distribution. The knowledge gained and resources developed through the Education Program grants are being utilized in the development of a national education campaign targeting consumers and health professionals. The NCI has provided funding to the CDC to plan and implement this campaign. The planning phase, already underway, includes representatives of the patient advocacy community and representatives of the federal and nonfederal research organizations involved in DES-relevant research and health education.

As a follow-up to a workshop held in 1992 (*NIH Workshop on Long-Term Effects of Exposure to Diethylstilbestrol),* NCI organized a workshop (*DES Research Update 1999, Current Knowledge, Future Directions),* held at NIH in July 1999. The 1 ½-day workshop involved about 175 participants, including academic researchers, government scientists (from NCI, NIEHS, and other NIH Institutes and Offices, the CDC, and the DHHS Office on Women's Health), and DES advocates and organizations. The purpose of the meeting was to disseminate information acquired from ongoing DES projects, to evaluate activities and achievements associated with recommendations from the 1992 workshop, to identify unmet research and data needs, and to discuss potential opportunities for further research. The agenda included overview sessions on basic laboratory research, epidemiologic studies, clinical research, and education and outreach research and activities focused on DES. Breakout sessions in these areas included discussions of the current and future needs for DES-related research and recommendations for addressing those needs. A poster session provided an opportunity to discuss recent research findings and also encouraged the participation of younger researchers. The proceedings of the workshop have been published and are currently available through the Cancer Information Service (1-800-4-CANCER). The complete text of the proceedings will shortly be available online on the NCI website.

Item

Complementary and Alternative Cancer Therapies -- The Committee expects NCI to work collaboratively with the National Center for Complementary and Alternative Medicine to support expanded research on promising complementary and alternative cancer therapies as well as on their integration with traditional therapies. Thousands of Americans are turning to these therapies, and consumers will benefit from the rigorous scientific review of these therapies. The Committee would like to be briefed on the progress of the Institute's efforts prior to the next appropriations cycle. (p. 116)

Action taken or to be taken

Please refer to pages NCI - 60 through NCI - 63 of this document for NCI's response to this significant item regarding Complementary and Alternative Cancer Therapies.

Item

Outreach and Public Education -- The Committee commends the NCI's dedication to the National 5-A-Day Campaign. This campaign is an important facet of NIH's overall commitment to the prevention of nutrition-related disease. The practical value of research is dependent on the translation of that research into practice by the public. The Committee recognizes that a diet including a minimum of five servings of fresh fruits and vegetables is a critical factor in reducing cancer risk. The Committee encourages NCI to substantially increase its communications and communications research for the 5-A-Day Program from its previous levels and increase its research in fruit and vegetable nutrition. (p. 116)

Action taken or to be taken

The NCI supports behavior change and communications research to determine effective strategies for increasing fruit and vegetable consumption. In light of this objective, the NCI and its award-winning 5-A-Day Program have conducted extensive consumer research to better understand motivators and barriers to eating more fruits and vegetables. In addition, NCI-supported communications research has provided valuable information on how best to reach target audiences. For example, NCI has been able to pinpoint areas of opportunity to reach the public when they are most likely to be receptive to health messages and to making a change in their eating behavior. Communications research also has been used to build and expand media outreach in an effort to increase the public's knowledge and awareness of the importance of eating at least 5 servings of fruits and vegetables for cancer control. This research has shed light on a range of issues, including health benefits, accessibility, and cost, and has shaped a variety of program components, from messages reinforced in brochures, campaign theme lines, and media materials to consumer tips and suggestions found in grocery stores. For example, understanding consumer attitudes has provided a solid foundation for information and tips that are found on a World Wide Web site that NCI created in partnership with the Centers for Disease Control and Prevention in 1998. This website (http://www.5aday.gov) is designed to encourage fruit and vegetable consumption and physical activity. It enables individuals to enter their daily consumption and activity, then analyzes the results and provides tailored information. It has been heavily promoted in several media campaigns and has drawn considerable public response. Efforts are currently underway to update the 5-A-Day website and make it more user-friendly and informative to the public.

Since 1991, NCI has conducted yearly surveys to track awareness of the 5-A-Day message. Results show that consumer awareness of the need to eat five or more daily servings of fruits and vegetables has more than quadrupled since the beginning of the program, from 8 percent in 1991 to 40 percent in 1999. However, further research is needed on nutrition-based community interventions and behavioral modification for underserved, minority population groups, as well as on long-term maintenance of dietary behavioral change relevant to cancer control. CD-ROM, the Internet, television, and focused, tailored messages specific to the needs of the individual are currently being explored as means to address these issues.

Studies of community interventions to increase fruit and vegetable consumption also have been very promising. Research to develop and test strategies for increasing fruit and vegetable consumption demonstrated a significant increase in fruit and vegetable intake among specific populations, including work sites, schools, and churches, as well as among participants in supplemental food programs. This research and other research in nutrition and behavior change begin to address critical nutrition-related questions for cancer control.

Current and Future Plans

To stimulate further research, the Health Promotion Research Branch in NCI's Behavioral Research Program hosted the first Nutrition and Behavior Research Grantees' Meeting on September 27-28, 1999 at the Dulles Hyatt Hotel, Herndon, VA. The purposes of this

conference were to bring together active researchers and NCI program staff, review current research findings, share lessons learned, and discuss the state of the science and new directions.

In 1999, the NCI formed the 5-A-Day Program Evaluation Group to provide a comprehensive review and assessment of the 5-A-Day Program and its efforts to date. This will be an interdisciplinary group, which will make recommendations to NCI's Board of Scientific Advisors. A formal report is expected by Fall, 2000. In tandem with this effort, the 5-A-Day Program is also undergoing a thorough review and evaluation of data collected since 1991 by NCI on the 5-A-Day Program.

Additionally, in 1998, the NCI appointed an internal working group to review the literature and determine gaps in knowledge in nutrition and physical activity research. The recommendations of this group will guide research initiatives in the future. A report is due in Spring, 2000. Research priorities that have been identified include:

I. Determinants of dietary behavior and change process
II. Methodological research
III. Research on diffusion and dissemination of scientific knowledge gained from studies, to the community level programs
IV. Policy, environmental, and organizational interventions focused on improving American's diets

NCI is committed to supporting the spectrum of research addressing fruit and vegetable consumption for cancer control. The following table provides dollars spent in fiscal year 1998 (actual) and fiscal year 1999 (estimated operating level) on research, communications, and evaluation for the 5-A-Day Program.

Component	**Fiscal Year 1998**	**Fiscal Year 1999**
Research Project Grants*	$ 2,759,000 ***	$ 3,272,000 ***
State Health Agency Research**	500,000	650,000
Communications	922,000	1,050,000
Evaluation	250,000	250,000
Total	**4,431,000**	**5,222,000**

* Investigator-initiated R01s
** Funded by NCI via interagency agreement with the Centers for Disease Control and Prevention
*** (1) Gimme 5--Interactive Multimedia Education
(U. TX M.D. Anderson Cancer Ctr., ended in fiscal year 1998)
(2) 5-A-Day Cafeteria Power Plus Program (MN State Dept. Of Health)
(3) Healthy Eating for a Lifetime Program (U. MD)
(4) CIS Research Consortium-Project 1 (AMC Cancer Research Ctr.)
(5) Motivating Dietary Changes in Churches
(Fred Hutchinson Cancer Research Ctr.)
(6) Weight Control to Prevent Cancer in African Americans (Memorial Hospital of RI)

Although the original set-aside Request for Application (RFA) mechanism for the 5-A-Day program ended in 1996, NCI continues to fund research in this area. Investigators incorporate the 5-A-Day message and strategies to increase fruit and vegetable consumption in their study designs, and NCI funds these studies via the research project grant (R01) competitive award mechanism. An excellent example of the diffusion and dissemination of the 5-A-Day research focus has been seen in the recent NIH Office of Behavioral and Social Sciences RFA on "Innovative Approaches to Disease Prevention Through Behavior Change," developed in partnership with the NCI and other NIH institutes. Two of the 15 grants funded in fiscal year 1999 contain a nutrition/behavior component modeled after the 5-A-Day Program (see descriptions below). These grantees had previously received NCI research funding through R01 or State Health Agency 5-A-Day research awards.

Youth Environments Promoting Nutrition and Activity

Social cognitive theory is utilized to predict that 7th and 8th grade educational curriculum interventions promoting fruit and vegetable consumption as well as increased physical activity will change the behavior of these students as they enter the 9th grade. This study is of particular interest in that it addresses issues of nutrition and increased physical activity for young teenagers.

Health Promotion through Black Churches

A randomized controlled trial conducted in cooperation with African-American churches in the Atlanta, GA area will test the effectiveness of a culturally sensitive self-help nutrition and physical activity intervention, implemented with and without ongoing brief motivational interviewing contacts by telephone to encourage maintenance of target health behaviors. The target health behaviors -- increasing physical activity and increasing dietary intake of fruits and vegetables -- are relevant to a number of health conditions (e.g., dental caries, cardiovascular diseases, cancer). Recruitment and assessments will occur during health fairs sponsored by these churches for their respective congregations. This intervention holds special promise for developing intervention approaches which can be incorporated into ongoing social structures, and which may be maintained in some form even after outside research funding ceases.

Communications efforts in partnership with the NCI's Office of Cancer Communications and the Produce for Better Health Foundation are a significant part of the 5-A-Day Program.

The following are the major 5-A-Day communications activities for fiscal year 1999. Plans are in place to continue or expand these activities in fiscal year 2000.

Radio Programming

For the past several years, NCI has developed and distributed radio programs through a partnership with chef Graham Kerr. The radio segments enable behavior change by providing practical tips to eat more fruits and vegetables. To date, there are more than 465 confirmed stations airing the segments, including nationally syndicated health shows. In addition, segments

are fed to more than 2,400 stations through radio networks such as CBS Radio and AP Radio. NCI will continue with the development and distribution of new radio spots this year.

Television Programming

NCI has developed broadcast news segments with chef Graham Kerr, a personality who has been shown to appeal to the 5-A-Day target audience. The content of the 90-second TV segments are similar to the radio spots described above. The TV segments are designed for stations to run twice a week throughout the year. Currently, the segments are broadcast by 15 television markets nationwide. Efforts to broaden market reach continue with cities like Los Angeles; San Diego; Denver; Chicago; Toledo, OH; Pensacola, FL; Tallahassee, FL; Panama City, FL; and Soldiers' TV, a network of the Armed Forces.

National 5-A-Day Week

National 5-A-Day Week, held on September 12-18, 1999, is a high-profile promotion for the 5-A-Day program. NCI developed and distributed a media package with the theme, "Get Fit with 5-A-Day." Additionally, NCI provided 5-A-Day Week materials to the 5-A-Day state coordinators for their local efforts.

Seasonal Print Media Outreach for Summer and Winter

One of the most effective means to maintain the continued presence of the 5-A-Day message in the media has been the extremely successful seasonal outreach packages for print media. This year's seasonal media outreach will include summertime and winter holiday story ideas. Components will include research, graphics, recipes, and tips.

Web Site Update, Outreach and Maintenance

In fiscal year 1998, NCI and CDC joined to create a 5-A-Day/physical activity Web site. The Web site includes tailored messages that consumers receive upon completing a tracking chart. NCI plans to further develop the Web site to include more tailored messages based on the stages-of-change theory. Since its development, it continues to draw positive audience response. When highlighted in a September 12, 1999 Parade Magazine Article, hits to this web site jumped from 3000+ per week to over 60,000+ per week in the two weeks following the publication of the article.

Three-Market Media Test

With the recent launch of the TV segments, awareness of the 5-A-Day message is likely to increase in the markets in which it is shown. NCI plans to conduct a media test to measure awareness levels in markets using the TV segments versus markets not using the segments.

5-A-Day Communications Research

To continue to mark the progress of the 5-A-Day media campaign, NCI will track awareness and attitudes among the target audience through several research methods, including focus groups and omnibus surveys.

Research and Communications Training for State Health Agencies

In July 1999, NCI provided training to the 5-A-Day community coordinators (including 55 state and territorial coordinators, and U.S. Military Health Promotion Professionals) at the Society for Nutrition Education Annual Meeting. This meeting included dissemination of promising research findings from NCI-funded behavioral change research and new strategies in 5-A-Day communications and media for use in the community. The key nutrition professionals present from each state and branch of the military served as the conduit to diffuse cutting edge research from the NCI.

In keeping with the public/private partnership intervention model, extensive possibilities for nutrition program partnering at the community level were discussed with the Centers for Disease Control, American Cancer Society, American Heart Association, National Heart Lung and Blood Institute, Produce for Better Health Foundation, and the U.S. Department of Agriculture.

Item

Pancreatic Cancer --The Committee is concerned that pancreatic cancer is not diagnosed until advanced stages when treatment options are limited and largely ineffective. The Committee expects the NCI to be prepared to report at next year's hearing on the Institute's commitment to support the development of early detection methods, improved surgical techniques, effective chemotherapy, and new drugs for pancreatic cancer and to support public education efforts concerning pancreatic cancer. (p. 116)

Action taken or to be taken

Please refer to pages NCI - 117 through NCI – 119 of this document for NCI's response to this significant item regarding Pancreatic Cancer.

Item

[Increased funding cancer research] -- The Committee is concerned that given the aging of the American population, the United States will face an explosion of cancer cases and deaths by 2010. According to the Research Task Force of the September 1999 Cancer March, by 2010, there could be a 29 percent in cancer incidence and a 25 percent increase in cancer deaths, at a cost of over $200,000,000,000 per year. This group of widely respected scientists recommended that cancer research be funded at $10,000,000,000 by 2005. The Committee looks forward to working with the cancer community and the NIH to increase funds for cancer research as recommended by the Research Task Force. (p. 116)

Action taken or to be taken

Aging of the U.S. population and of other major industrial nations is a trend that continues to reshape our global demographic, social, economic, political, and cultural structures. Longer life spans, dramatic changes in disease patterns, and the ongoing revolution in biotechnology are reshaping health-related perspectives. Within this broader context and coupled with simultaneous changes in the racial and ethnic composition of our populations, national trends in the U.S. cancer burden are in flux.

Many times it is difficult to understand the inter-relationships of the burden of the disease on a population and the risk of having/dying of a disease. Cancer is predominantly a disease of older Americans with 60 percent of all diagnosed cases and 70 percent of all cancer deaths occurring among persons 65 years and older. The median age at cancer diagnosis is 68 years of age and at 71 years of age for cancer death. A recent article showed that between 1990 and 1996, cancer incidence rates decreased an average of about 1 percent per year and mortality decreased an average of 0.6 percent per year. While the rates have decreased, the trends in number of cancer cases is more unpredictable, and the number of cancer deaths has increased because there are more people in the United States and the population is aging.

Demographers have projected that the population will continue to increase and to age. Between 1997 and 2010, the population will increase 11.2 percent; the <65 age group will increase 10.6 percent and the 65+ age group will increase 15.2 percent. Unless there are really steep declines in the cancer incidence and mortality rates, this means that we will continue to see increases in the overall numbers of cases and deaths. This also means that cancer will continue to be an increasing burden on our health care systems for the foreseeable future.

Current Activities:

- A study at Harvard focuses on the age-related impact of breast cancer on physical and psychosocial function, comparing older and younger women.
- A cohort study in Iowa study addresses potentially modifiable risk factors for breast cancer in older women, and another project is assessing the effect of exercise breast cancer risk in older women. Multiple studies assess endogenous hormone levels in older women and breast cancer risk.
- A series of projects is addressing the adverse effects, protective effects, and risk modification by therapeutic drugs, both by prescription and nonprescription, taken by older men and women, since medication use increases with age. One study assesses commonly used medications and breast cancer risk in a biracial population. Another project focuses on calcium channel blockers, increasingly used for hypertension and coronary disease in older women, as well as other medications, and the risk of breast cancer. Other projects are looking at postmenopausal hormone therapy in older women and the risk of endometrial cancer, large bowel cancer, mammographic density changes, and breast cancer in multiple ethnic groups.
- Prostatic intraepithelial neoplasia (a potential precursor of prostate cancer) is being studied in older men in several different ethnic groups.
- Total hip or knee replacement becomes more common with aging. One project is studying hip or knee replacement with devices containing chromium, to assess the degree to which

DNA-protein crosslinks are generated, a sign (biomarker) of biologic damage from chromium exposure.

- A large follow-up study is looking for predictors of general cancer mortality in an aging cohort first studied over thirty years ago.
- Several cancer-screening studies are developing behavioral interventions to overcome older women's barriers to getting screened for breast and cervical cancer.
- The NCI has joined with the National Institute on Aging (NIA) to conduct two studies on aging and cancer. The first study was a retrospective review of medical records to assess other conditions that lead to morbidity in three age strata (55-64, 65-74 and 75+ years of age) of cancer patients. The second study is an illness behavior study, which includes patient interviews to assess comorbidity and functional status. Several analyses have been published on the first study and other analyses are in progress. The second study has completed data collection. The major objectives of these studies are to develop descriptive information in response to two basic questions: 1) What are the predominant comorbid conditions and functional limitations for older persons with cancer? And 2) What do older persons do when they become aware of having suspicious signs and symptoms?
- The SEER-Medicare database, a collaborative effort of the NCI, the SEER registries, and the Health Care Financing Administration, is a large population-based source of information for cancer-related epidemiologic and health services research. This database, which contains information on cancer cases from 1986 through 1996, allows researchers to address topics such as the economics of cancer care, patterns of care from diagnosis through end of life, variation in care across diverse health care systems, and changes in cancer care over time. In 1999, 14 articles using SEER-Medicare data have been published. The focus of these papers has included comparisons of cancer care between persons with fee-for-service (FFS) coverage vs. HMO care, factors that influence the reported changes in cancer incidence, patterns of cancer care, and methodological evaluations of the utility of Medicare claims for cancer surveillance. The findings from the HMO and fee-for-service comparisons are varied. In the case of prostate cancer, men with FFS coverage have better cancer-specific survival than men in HMOs, while for colon cancer, cancer-specific mortality was comparable between persons with FFS and HMO coverage. Perhaps the most noteworthy conclusion from two of these studies is that there is considerable variation in treatment patterns between individual HMOs. As a result, findings from studies comparing care from an aggregation of HMOs with an aggregation of cases provided to person with FFS coverage may have limitations in the ability to extrapolate findings to all HMOs.

Future Activities (some already underway):

- The NCI and the NIA are jointly supporting a series of collaborative and interdisciplinary genetic epidemiology investigations. These studies are designed to identify and evaluate the interactions of genetic and epidemiologic risk factors leading to cancer susceptibility in individuals, families and populations, as well as factors influencing the rate of increase with age in cancer susceptibility. The special feature of this Request for Applications (RFA) is the support of multi-site, cooperative research applications by multi-disciplinary teams of investigators. Particular attention is to be paid to aging populations and to the genetic factors leading to older age at onset of cancer.

- A population-based cohort study has just been launched to examine the broad impact of variation in candidate genes and their interaction with environmental exposures on cancer incidence and survival specifically, and health and aging more generally. Participants, numbering 8395 people, from two blood and data specimen banks CLUE I (1974) and CLUE II (1989) comprise the study cohort. The cohort has been followed prospectively for 24 years and information on environmental factors such as smoking, education, and housing are available as far back as 1963.
- Breast cancer with an onset at older ages is probably caused by the interaction of multiple genes, endogenous environments, and exogenous exposures. One consequence of this complex, multifactorial etiology of breast cancer is that etiologic heterogeneity may exist. A recently launched project is addressing this question. Etiologic heterogeneity implies that two or more types of breast cancer in the general population may be caused by different sets of etiologic events. The ability to define etiologically-distinct (i.e., homogeneous) subgroups in the population may facilitate: 1) epidemiological studies to identify causative agents in breast cancer etiology; 2) identification of optimal breast cancer diagnosis or treatment regimens; and 3) the targeted application of cancer detection and prevention strategies. Cancer susceptibility genotypes at the cytochromes p450 and glutathione-S-transferase loci, as well as somatic genetic mutations, will be evaluated for their capacity to define etiologically heterogenenous case groups with respect to age at breast cancer diagnosis.

Research priorities that have been identified with regard to the development of cancer in an aging population include improving the accuracy of our measurement and estimation of exposure. Particularly, historical exposures years ago in childhood, and exposures that occur long term and over the entire lifespan, to environmental agents, need to be accurately assessed. Our approaches to study design and analysis for conducting environmental research that focuses on lifespan gene-environment interactions need to be improved.

As we begin the 21st century, we are without doubt in a position to make real improvements in human health and disease. We made remarkable progress in the 20th century in our knowledge of cancer biology, dramatically expanding our understanding of what is required to turn a normal cell into a cancer cell. Recently developed molecular-based technologies are providing even greater insights into the steps involved in the transformation of cells from normal to precancerous to cancerous, allowing us to detect and diagnose cancers much earlier. Other advances in technology, such as new and enhanced imaging tools and techniques, coupled with new drugs, targeted therapeutic interventions, and new insights and discoveries into the fundamental nature and causes of cancer, present unprecedented opportunities for advancing our understanding of cancer and improving quality of life for people diagnosed with cancer.

NCI's role is to provide the vision creative environments, and diverse resources needed to ensure a smooth flow between the increasing number of discoveries and advances in cancer research and the scientific community's ability to apply these findings to prevent and treat the many forms of cancer.

NCI conducts, coordinates, and funds cancer research, and provides vision and leadership for the cancer research community. NCI supports this vital work through research programs that seek answers to the many remaining questions about how best to prevent and treat cancer. Pursuing

these answers can take one of two interrelated and complementary paths – studying the cancer cell itself to uncover biological processes broadly applicable to all cancers, or studying one of the more than 100 specific types of cancer. Though these research approaches appear to be divergent, they are inextricably linked, and in fact, most fruitful when there is extensive interplay and cross-fertilization between them. As cancer researchers develop an understanding of biological processes common to many tumor types, we gain new knowledge that can be applied to cancer-specific research, and as we make discoveries about a specific cancer, new questions about themes common to all cancers are prompted.

A substantial increase in cancer funding would allow NCI and the nation to jump start the expansion of further exploring the extraordinary opportunities and emerging technologies in the field of cancer research. More funds will lead to a broader expansion of research that will provide quicker, more extensive interplay and cross fertilization of ideas, questions and knowledge of cancer.

NCI will continue to establish the mechanisms that will allow the scientific community to apply these discoveries and emerging technologies to the field of cancer research. These mechanisms will promote and reward innovative thinking, the cross-fertilization of ideas among disparate scientific disciplines, and enhanced collaborations among government, academia, and industry.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2000 Amount Authorized		2000 Estimate	2001 Amount Authorized		2001 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite			Indefinite		
				>	$3,007,412,000		>	$3,189,235,000
National Cancer Institute	Section 410 etseq.	42§285	Indefinite			Indefinite		
National Research Service Awards	Section 487(d)	42§288	a/		59,781,000	b/		60,495,000
Total, Budget Authority					3,067,193,000			3,249,730,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2000, as enacted by Section 1000 (a)(4) of the Consolidated Appropriations Act, 2000 (P.L. 106-113)

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1992	$1,810,230,000	$1,830,509,000	$2,010,230,000	$1,962,587,000 2/
1993	2,010,439,000	1,998,616,000	2,010,439,000	1,981,351,000 3/
1994	2,142,122,000	2,082,267,000	2,082,267,000	2,076,382,000
1995 4/	1,967,709,000	1,917,929,000	1,917,929,000	1,919,419,000 5/
Rescission				(5,600,000)
1996	1,994,007,000 4/	2,251,084,000	2,184,467,000 4/	2,251,084,000
Rescission				(2,654,000)
1997	2,060,392,000 4/	2,385,741,000	2,102,949,000 4/	2,381,399,000 6/
1998	2,217,482,000 4/	2,513,020,000	2,558,377,000	2,547,314,000
1999	2,528,760,000 4/7/	2,787,830,000	2,927,187,000	2,927,187,000
Rescission				(1,940,000)
2000	2,732,795,000 4/	3,163,417,000	3,286,859,000	3,332,317,000
Rescission				(17,763,000)
2001	3,249,730,000 4/			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes enacted administrative reductions of $22,255,000; $482,000; and $3,954,000.
3/ Excludes enacted administrative reductions of $16,060,000; $9,933,000; and $139,000.
4/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS R
5/ Excludes enacted administrative reductions of $901,000; $116,000; and $1,482,000.
6/ Excludes enacted administrative reductions of $1,095,000 and $38,000.
7/ Reflects a decrease of $7,301,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTE)

OFFICE/DIVISION	FY 1999 Actual	FY 2000 Estimate	FY 2001 Estimate
Office of the Director	648	688	688
Division of Basic Sciences	566	800	830
Division of Cancer Biology	46	62	62
Division of Clinical Sciences	560	642	663
Division of Extramural Activities	87	103	103
Division of Cancer Treatment and Diagnosis	195	220	220
Division of Cancer Prevention	75	90	90
Division of Cancer Control and Population Sciences	94	112	112
Division of Cancer Epidemiology and Genetics	122	140	140
Total, NCI	2,393	2,857	2,908
Statutorily-ceiling exempt FTEs not included above	5	5	5
Funds to support these FTEs are provided by Cooperative Research and Development Agreements			

FISCAL YEAR	Average GM/GS Grade
1997	10.9
1998	11.1
1999	11.2
2000	11.1
2001	11.1

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Program Administration

Detail of Positions

GRADE	FY 1999 Actual	FY 2000 Estimate	FY 2001 Estimate
ES-6	2	2	2
ES-5	3	3	3
ES-4	5	5	5
ES-3	1	1	1
ES-2	3	3	3
ES-1	2	2	2
Subtotal	16	16	16
Total - ES Salary	$1,947,103	$2,017,199	$2,105,955
GM/GS-15	262	290	292
GM/GS-14	275	310	315
GM/GS-13	225	260	265
GS-12	336	375	378
GS-11	232	260	270
GS-10	10	15	15
GS-9	154	222	235
GS-8	151	165	165
GS-7	163	185	190
GS-6	57	60	60
GS-5	42	50	50
GS-4	35	36	36
GS-3	6	8	8
GS-2	4	5	5
GS-1	0	0	0
Subtotal	1,952	2,241	2,284
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	66	69	70
Senior Grade	37	41	46
Full Grade	37	37	38
Senior Assistant Grade	1	1	1
Assistant Grade	0	0	0
Co-Step	0	0	0
Subtotal	142	149	156
Ungraded	456	499	500
Total permanent positions	2,054	2,329	2,372
Total positions, end of year	2,566	2,905	2,956
Total full-time equivalent (FTE) employment,end of year	2,393	2,857	2,908
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$121,694	$126,075	$130,800
Average GM/GS grade	11.2	11.1	11.1
Average GM/GS salary	$58,458	$59,703	$61,900

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
New Positions Requested

	FY 2001		
	Grade	Number	Annual Salary
Administrative Asst	GS 9	1	$42,000
Administrative Officer	GS 12	1	62,000
Bio Lab Tech	GS 7	1	35,000
Bio Lab Tech	GS 9	1	42,000
Bio Lab Tech	GS 11	1	51,000
Biologist	GS 7	2	35,000
Biologist	GS 9	5	42,000
Biologist	GS 11	2	51,000
Biologist	GS 12	1	62,000
Biologist	GS 13	1	73,000
Chemist	GS 9	3	42,000
Chemist	GS 11	1	51,000
Geneticist	GS 12	1	62,000
Geneticist	GS 14	1	86,000
Investigator (Tenure Track)	AD -	1	80,000
Lab Manager	GS 9	1	42,000
Lab Manager	GS 11	1	51,000
Manager Admin Resource	GS 14	1	86,000
Medical Officer	GS 13	1	77,000
Medical Officer	GS 15	1	104,000
Medical Technologist	GS 9	1	44,000
Microbiologist	GS 7	1	35,000
Microbiologist	GS 9	1	42,000
Microbiologist	GS 11	1	51,000
Microbiologist	GS 12	1	62,000
Microbiologist	GS 13	2	73,000
Molecular Biologist	GS 9	2	42,000
Molecular Biologist	GS 11	1	51,000
Molecular Biologist	GS 12	1	62,000
Molecular Biologist	GS 14	1	86,000
Procurement Tech	GS 7	1	32,000
Secretary	GS 5	1	26,000
Secretary	GS 7	1	32,000
Senior Biologist	GS 15	1	102,000
Senior Clinical Investigator	GS 14	1	86,000
Senior Clinical Investigator	SBRS -	1	113,000
Senior Molecular Biologist	SBRS -	2	116,776
Senior Research Chemist	GS 15	1	102,000
Senior Research Geneticist	SBRS -	1	117,936
Senior Research Virologist	SBRS -	1	118,000
Total Requested		51	