DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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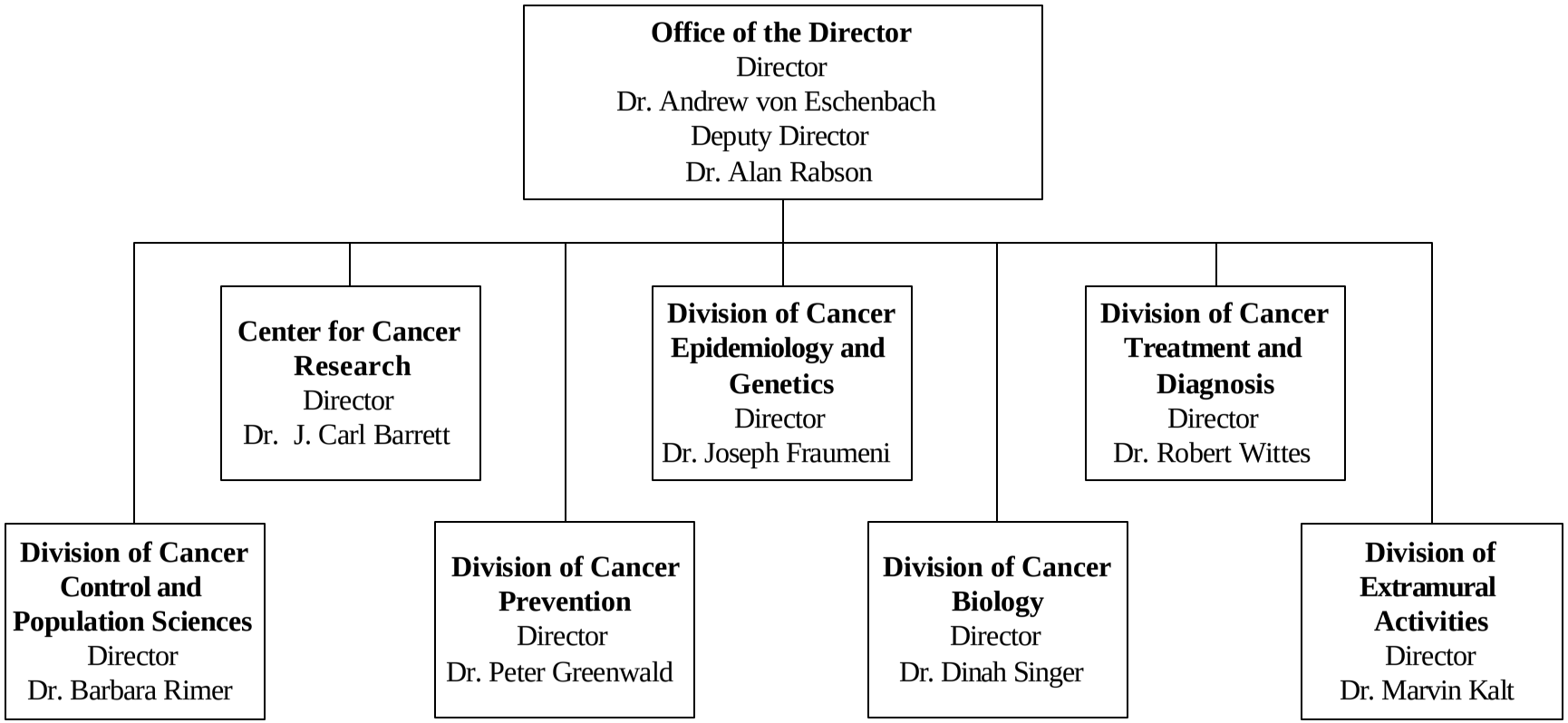
Organization Chart



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, [$4,190,405,000] *5,122,111,000*: Provided, that the Director of the National Institutes of Health may transfer up to $397,606,000 to other National Institutes of Health appropriations: Provided further, that total amount provided for cancer research at the National Institutes of Health will not be less than $5,122,111,000.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act for Fiscal Year 2002, (P.L. 107-116)]

National Institutes of Health

National Cancer Institute
Amounts Available for Obligation 1/ 3/

Source of Funding	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Appropriation	$3,757,242,000	$4,190,405,000	$5,100,000,000
Enacted Rescission	(2,005,000)	(2,054,000)	---
Subtotal, Adjusted Appropriation	3,755,237,000	4,188,351,000	5,100,000,000
Comparable adjustment for legislative proposal for accrued retirement costs	19,218,000	21,370,000	22,111,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(711,000)	---	---
Real transfer to HHS for the Office of Human Research Protection	(781,000)	---	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	1,643,000	---	---
Comparative transfer to:			
Other NIH Institutes for research activities	---	---	(397,606,000)
National Institute of Biomedical Imaging and Bioengineering	(21,153,000)	---	---
National Institute of Allergy and Infectious Diseases for the Vaccine Research Center	(18,171,000)	---	---
Subtotal	3,735,282,000	4,209,721,000	4,724,505,000
Unobligated Balance, start of year 2/	3,752,000	---	---
Revenue from Breast Cancer Stamp 2/	5,556,000	---	---
Unobligated Balance, end of year 2/	(4,463,000)	---	---
Subtotal, adjusted budget authority	3,740,127,000	4,209,721,000	4,724,505,000
Unobligated balance, lapsing	(24,000)	---	---
Total obligations	3,740,103,000	4,209,721,000	4,724,505,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2001 - $10,972,000; FY 2002 - $10,972,000; FY 2003 - $10,972,000
Excludes $27,187,000 in FY 2001 and $20,000,000 in FY 2002 for royalties.
Excludes $37,000 for reimbursable accrued costs.

2/ Stamp Out Breast Cancer Act P.L.#105-41

Justification

National Cancer Institute

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

Budget Authority:

	2001 Actual	2002 Appropriation	2002 Current Estimate	2003 Estimate	Increase or Decrease
Current Law BA	$3,720,909,000	$4,190,405,000	$4,188,351,000	$4,702,394,000	$514,043,000
Accrued Costs	$19,218,000	$21,370,000	$21,370,000	$22,111,000	$741,000
Proposed Law BA	$3,740,127,000	$4,211,775,000	$4,209,721,000	$4,724,505,000	$514,784,000
FTE	2,979	3,150	3,150	3,188	38

This document provides justification for the Fiscal Year 2003 activities of the National Cancer Institute (NCI), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2003 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The President's appropriations request of $4,724,505,000 for this account includes current law adjusted by assuming Congressional action on the proposed Managerial Flexibility Act of 2001.

Introduction

As we reflect on the advances made in our fight against cancer since the National Cancer Act was adopted in 1971, we realize how far we have come. Whereas 30 years ago, some predicted that with the right level of resources, we could cure cancer in 5 years, we now know that cancer is a complex set of diseases for which there is no single cure. Scientists have learned that cancer results from a variety of genetic changes and have identified numerous hereditary, environmental, lifestyle, and infectious agents that lead to or contribute to cancer. In spite of these complexities, we have made enormous strides:

- Today, we cure or increase life expectancy for more than half of all cancers.
- We have more options for prevention, including chemoprevention, and are developing more evidence-based interventions for cancer control.
- We are much more attuned to the importance of detecting cancer early, and physicians are armed with a variety of sophisticated detection tools.
- Cancer treatment is improving dramatically, saving lives, often with treatments that are much less invasive than in the past.
- We continue to extend survival and are working to ensure that cancer patients have the longest possible period of high-quality life.

That is the encouraging news. The bad news[1] is that

- In spite of declining incidence rates overall, more than one million people are newly diagnosed with cancer in the United States each year. One of every two men and one of every three women develop cancer over the course of their lives.
- The incidence of some cancers – such as esophageal, melanoma, and lung cancer in women – is still rising.
- Nearly 25 percent of all deaths in our country are due to cancer. Cancer is the second leading cause of death in the United States, ranking behind only heart disease.
- Many of the well over eight million Americans who have survived cancer continue to suffer from an array of physiological and psychosocial side effects, a number of which are severely debilitating or even life threatening.
- The cost of cancer treatment continues to rise. Medical care expenses for cancer patients and survivors add up to $60 billion annually, about 5 percent of all dollars spent on health care in the United States.
- Americans are not yet effectively addressing some major established risk factors for cancer. For example, youth smoking has been on the rise, people are not doing as much as they could to protect themselves from the sun, and more people are overweight and obese.

SCIENTIFIC ADVANCES

NCI-supported research continues to yield results in our quest to discover better ways to prevent and control, detect and diagnose, and treat cancer.

Preventing and Controlling Cancer

Investigators Quantify the Risk of Pancreatic Cancer in Relatives of Pancreatic Patients
Though oncologists have known for some time that pancreatic cancer runs in some families, the extent of this trend and the reasons behind it have been much less clear. To learn more about the potential for genetic susceptibility to pancreatic cancer NCI-sponsored investigators followed nearly 350 families of patients with pancreatic cancer over a 6-year period. These researchers determined that individuals with two or more first-degree relatives (siblings, parents, and children) with pancreatic cancer are at 18 times higher risk of developing the disease themselves than those in the general public. For those with three or more relatives with pancreatic cancer, an extremely rare occurrence, the risk is 57 times that of the general public. These findings provide the first quantitative measure of risk for pancreatic cancer and will help identify individuals who could benefit from pancreatic screening and preventive measures.

Better Understanding of Juvenile Polyposis May Lead to Better Cancer Prevention
Juvenile polyposis (JP) is a hereditary disease in which growths begin forming during childhood in various portions of the digestive tract, including the stomach, small intestine, and colon. The

[1] This information is taken from three sources: *Cancer Facts and Figures 2001,* American Cancer Society; *Annual Report to the Nation on the Status of Cancer 1992-1998,* a collaborative effort of the National Cancer Institute, the Centers for Disease Control and Prevention, The National Center for Health Statistics, the American Cancer Society, and the North American Association of Central Cancer Registries; and the *Cancer Progress Report*, National Cancer Institute, 2001.

polyps can cause bleeding and damage in the intestine, and afflicted individuals have a 50 percent risk of developing gastrointestinal cancer. To prevent cancer from developing, people with the condition must have life-long monitoring of the gastrointestinal tract to identify polyps to be removed surgically or undergo surgery that removes portions of the gastrointestinal tract. Previously, scientists identified mutations of a gene that caused JP in about 20 percent of the patients. Researchers studying families that lack these known mutations have found compelling evidence that another gene may be causing JP in a second subset of patients. Researchers identified a suspicious mutation in the gene *BMPR1A* which produces the receptor protein BMPR1A, distributed widely throughout the body. This receptor serves as a base for the protein, BMP, which regulates cell growth and appears to help control tumor growth. In this study, the researchers found that the *BMPRIA* gene was altered in people with juvenile polyposis in a way that disrupted BMP's activities and allowed polyps to form. Such information may permit presymptomatic screening in patients at risk for JP, may speed diagnosis, and suggests that new approaches other than surgery may be developed to control the syndrome. The findings also provide the first genetic evidence that BMP may play a key role in controlling some cancers.

Studies Provide Insight for Preventing Youth Smoking

Because most smokers take up the habit at a fairly young age, developing effective smoking prevention programs requires a thorough understanding of why young people start to smoke in the first place. In one of the largest prospective studies to ever examine smoking and personality, a group of scientists evaluated the extent to which the personality characteristics of more than 3,000 fifth graders would predict whether they would become smokers by the 12th grade. In tracking the students to their last year of high school, investigators found that the most significant predictors of smoking were rebelliousness and risk-taking behavior. Contrary to common perceptions, students' susceptibility to peer pressure did not predict smoking. In light of these findings, investigators concluded that smoking prevention programs for young people should start before fifth grade and be designed to address the needs of rebellious and risk-taking youth.

Long-Term Studies Clarify the Role of Low-Tar Cigarettes in Lung Cancer

Epidemiologic studies in the late 1960s and 1970s seemed to indicate that people who smoked lower-tar or filtered cigarettes had somewhat lower lung cancer risks than smokers of other cigarettes. However, as more smokers turned to these cigarettes, death rates from lung cancer in the United States, though expected to fall, continued to increase. These rates did not begin to fall until the early 1990s, after the percentage of adult smokers in the United States began to decline. To shed some light on these trends, the NCI recently issued *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine,* the latest in an ongoing series of monographs on smoking and tobacco use, summarizing and assessing research on low-tar cigarettes over the last 50 years. The monograph reviews several reasons why lung cancer rates continued to rise despite the use of low-tar cigarettes. Many smokers cover the vent holes in low-tar/low-nicotine cigarettes that are intended to allow air to dilute the smoke as it is inhaled. Furthermore, smokers who switch to low-tar or low-nicotine cigarettes often begin inhaling more deeply; taking larger, more rapid, or more frequent puffs; or smoking more cigarettes per day. As a result of these and other findings, the national panel of experts who authored the monograph concluded that smokers who choose lower-yield cigarettes are unlikely

to reduce their tar intake and resulting disease risks and that there is no public health benefit to low-tar cigarettes.

Racial and Ethnic Differences in Advanced-Stage Prostate Cancer Need Further Study
Investigators assessing results from the NCI-sponsored Prostate Cancer Outcomes Study, which is following over 3,000 men to learn more about the results of different therapies and their effect on quality of life, recently examined the racial and ethnic differences among men who develop advanced prostate cancer. The researchers found that African American men have the greatest risk of developing advanced disease (12.3 percent of study participants). This is higher than that of Hispanic men (10.5 percent) and about twice that of non-Hispanic Whites (6.3 percent). Differences in socioeconomic status, symptoms, and tumor characteristics seem to account for the differences between non-Hispanic Whites and Hispanics, but do not explain a significant portion of the African American disparities. NCI is initiating further research on biologic markers, genetic susceptibility, and additional socioeconomic factors such as use of health care systems, distance from health care, diet, literacy, and health beliefs to explain these disparities and determine how to use this information to reduce cancer risk for these populations.

Cancer Is Associated with AIDS-Related Immunosuppression in Adults
Persons infected with the human immunodeficiency virus (HIV) often have a weakened immune system, as do those with AIDS. A suppressed immune system places HIV-infected individuals at increased risk for three specific AIDS-defining cancers: Kaposi's sarcoma (KS), which affects the skin and can affect the lungs; non-Hodgkin's lymphoma; and invasive cervical cancer. Other cancers also appear to occur disproportionately in HIV-infected persons in industrialized parts of the world. However, the incidence of these non-AIDS-defining cancers varies by geographic region and HIV exposure group. In a large-scale study, scientists examined the general cancer patterns among more than 300,000 adults with HIV/AIDS from 11 different geographical regions of the United States in an effort to distinguish cancers associated with immunosuppression from other cancers occurring in excess among persons with HIV/AIDS. As expected, those with HIV/AIDS had an excess of AIDS-defining cancers. In addition, this population had elevated rates of several non-AIDS-defining cancers. Only Hodgkin's lymphoma and possibly lip cancer and testicular seminoa (a form of testicular cancer), however, met the three criteria set by the study authors for a genuine association with immunosuppression. Other cancers that occurred more frequently in AIDS patients, such as lung or penile cancers, probably developed not from immunosuppression but from lifestyle factors, such as heavy smoking or frequent exposure to the human papillomavirus.

New Insights into the role of BRCA1 and BRCA2 Mutations in Ovarian Cancer
In most families with breast-ovarian syndrome, mutations in the genes *BRCA1* and *BRCA2* account for their increased risk of developing cancer. Recently, to determine the role of these mutations in ovarian cancer in the general population, researchers screened for the most common *BRCA1* and *BRCA2* mutations in 649 ovarian cancer patients. The researchers did not find any of these mutations in women with non-invasive cancer, but found mutations in 11.7 percent of women with invasive cancers – higher than earlier estimates. Among these women, most who developed cancer before age 50 carried a *BRCA1* mutation, while those diagnosed after age 60 were more likely to have a *BRCA2* mutation. Risks of cancers, including ovarian, breast, stomach, leukemia and lymphoma, were increased between three- and nine-fold among first-

degree relatives of women who had *BRCA1* mutations, compared with relatives of non-carriers. The risk of colorectal cancer was three-fold higher for relatives of women with *BRCA2* mutations. This study has helped to clarify the contribution of *BRCA1* and *BRCA2* mutations in both early and late onset cancers, especially ovarian cancer. Past studies may have underestimated the contribution of *BRCA2* to ovarian cancer because these mutations cause mainly late onset cancer, and earlier work targeted early onset disease.

Vaccine Research Shows Promise for Preventing Human AIDS and Related Cancers
Progress in anti-retroviral therapy has led to a decrease in AIDS-related deaths in the United States However, patients living longer with compromised immune systems have an increase risk of developing many cancers. The search for a safe and effective preventive vaccine is a central goal for scientists working to control the HIV epidemic and its associated diseases. Despite the difficulties caused by variation in the virus and in identifying antigens that produce long-lasting immunity, this research has been greatly advanced by studies of the simian immunodeficiency virus (SIV), an HIV-like virus that infects monkeys.

In a recent simian AIDS vaccine trial, test monkeys received a vaccine containing DNA that codes for SIV proteins. In some animals, the vaccine was augmented with interleukin-2 proteins, which enhance immune response. When given a large intravenous dose of SIV, all of the vaccinated monkeys became infected with the disease. Monkeys who received only the DNA vaccine without IL-2 displayed significant clinical signs of disease, and 50 percent died within 140 days of infection. In contrast, monkeys who received the augmented vaccine demonstrated stable immune systems, low or undetectable viral loads, and no evidence of clinical disease or mortality. This is the first research to demonstrate that an SIV vaccine can prevent overt simian AIDS, raising the hope that a similar vaccination can be produced for humans. Vaccinated individuals might have decreased viral burdens, less disease progression to AIDS, lower rates of HIV transmission, and fewer cases of AIDS-associated malignancies.

Obesity and Hypertension Increase the Risk of Kidney Cancer Among Men
Renal-cell carcinoma, the most common form of kidney cancer, is one of the most rapidly increasing of all types of tumors in the United States, particularly among African Americans. Past research has suggested that obesity and high blood pressure might heighten the risk of developing renal-cell carcinoma. To clarify this relationship, researchers reviewed the medical records of more than 350,000 men who worked in the construction industry. Nearly 900 of the men had received a diagnosis of some type of kidney cancer. Comparing those who developed kidney cancer with those who did not, investigators found that the risk of renal-cell cancer was consistently higher in men with higher body mass indices (a measurement of the relationship of weight to height), and nearly double for those men in the highest eighth of the group for body-mass index compared to those in the lowest eighth of the group. Moreover, the scientists found that the risk of kidney cancer rose with increasing blood pressures and declined with decreasing blood pressures. These findings suggest that maintaining a healthy weight and blood pressure may help prevent this increasingly common form of cancer.

New Technique Appears to be Highly Accurate for Identifying Genetic Risk of Colorectal Cancer
About 20 percent of colorectal cancer patients may have a genetic susceptibility to this disease and scientists have identified specific inherited genetic mutations that appear to account for five

to six percent of colorectal cancer cases overall. Patients who test positive for one of these mutations can benefit from aggressive cancer screening programs. Unfortunately, conventional genetic testing may fail to detect these mutations in up to 50 percent of affected persons. Everyone carries two copies of each of his or her genes and conventional genetic tests analyze both copies at the same time. When only one copy of the gene is mutated it can be "masked," or hidden, by the second normal copy. Scientists recently developed a technology called "conversion" that prevents masking by separating the two copies of the gene before they are tested. In this technique, researchers unite samples of human cells with specially designed mouse cells in a way that some of the hybrid cells contain only one copy of the gene to be tested. The researcher can then use conventional methods to test just that copy of the gene for mutations. This technique is expected to remarkably increase sensitivity of cancer susceptibility testing and correctly detect nearly 100 percent of mutations for predisposition to certain colorectal cancers. Although so far tested only for colorectal cancer, conversion should work well for other cancers with hereditary susceptibility, such as breast and kidney cancer, as well as a wide variety of neurological and cardiovascular diseases.

Detecting and Diagnosing Cancer

Preliminary Study Shows Genetic Testing of Stool Samples Detects Most Colorectal Cancers
Colorectal cancer accounts for the second largest number of cancer deaths in the United States. Early detection improves survival, but the current detection methods are invasive. Because colorectal cancer cells are shed into the stool, testing stool samples for the presence of tumor-associated alterations can be an easy and non-invasive way to detect this disease. Colorectal cancer often has a fairly small number of genetic alterations affecting only three cancer-related genes. Recently, a team of investigators used genetic screening to accurately identify colorectal cancer in about three quarters of 51 patients known to have the disease. Researchers analyzed DNA from stool samples taken before surgical removal of the tumors and also in the excised tumor tissue. Using three different tests to detect tumor-associated mutations, scientists found that the presence of these altered genes in the stool samples accurately indicated cancer in 36 of the 51 patients, and in 36 out of 39 patients (or 92 percent of patients) whose tumors had one of these genetic alterations. No mutation was found in any stool sample that was not also found in that patient's tumor tissue. Although more studies are now needed to determine whether these alterations effectively detect colorectal cancer in patients without symptoms, the test may one day be a reliable and non-invasive early detection tool.

Biomarkers May be Useful in Detecting Early Ovarian Cancer
If ovarian cancer is detected before it spreads beyond the ovaries, the five-year survival rate is 93 percent. However, because early disease has few symptoms, fewer than 25 percent of the cases are detected early and less than 50 percent of women with this cancer survive longer than five years. In light of this, researchers are seeking sensitive and specific noninvasive techniques to improve the early detection of ovarian cancer. These efforts have advanced greatly as scientists have devised ways to identify and evaluate genes that are over-expressed in the disease. When a tumor cell makes more of any particular molecule, and if that molecule is secreted into the blood, it has the potential to be an easily accessed marker for the presence of the cancer. An ovarian tumor marker, CA-125, already is used in clinical practice to identify later-stage ovarian cancers and monitor patient response to therapy, but it is not useful for early detection. Now, scientists

have identified five genes – *mesothelin*, *HE4*, *ESE-1*, *SLPIa*, and *GPR39* – that are consistently overexpressed in ovarian tumors and produce molecules that are likely to be secreted into the blood. Scientists hope these markers will prove useful as biomarkers for early disease. Ultimately, this research could have a profound impact on the survival of patients with ovarian cancer.

New Microscope Provides a View of Living Cells
The best microscopes available to scientists today allow them to examine the molecular details of cells, but in order to do so, the cells must be treated with resins or dyes, which either kill the cells or fundamentally alter their behavior. Magnetic resonance imaging, on the other hand, allows physicians to view the functioning of the body, but its resolution cannot provide a view of individual cells. To capture the best of both instruments, a multidisciplinary team of NCI-funded physicists, biologists, optical experts, and chemists developed a new type of microscope combining the capabilities of nuclear magnetic resonance imaging with those of a traditional microscope. Using the combined microscope, investigators can examine how living cells react to changes in their environment, track the development of cancer, and study how cancer cells respond to treatment.

New Imaging Tools Provide More Accurate and Complete Diagnoses
NCI-funded scientists are developing imaging systems to make cancer detection more efficient and less invasive. New systems may permit patients to undergo "optical biopsies" in the future and allow physicians to diagnose cancer without the need for tissue samples. By modifying endoscopes and similar instruments used to examine the gastrointestinal system, lungs, and other internal organs so that they provide very high-resolution images, investigators can now identify the cellular changes typical of early cancer when it is most treatable. In cases where these more powerful images can rule out cancer, such "optical biopsies" will allow patients to avoid unnecessary and painful tissue biopsies. In a related development, two groups of NCI-supported investigators working to improve cancer screening recently received Food and Drug Administration approval for computer-aided diagnosis systems to help radiologists assess the results of mammograms and chest x-rays. In these systems, computers are programmed to identify and highlight suspicious "hot spots" to ensure that all potentially cancerous points are scrutinized.

Treating Cancer

Vaccines Show Promise Against Several Cancers
Scientists are learning to successfully use cancer vaccines to harness the molecular workings of the body's immune system to attack cancer cells and stop tumor growth with few side effects. Recent studies of metastatic melanoma provide some of the first examples of this success. In a preliminary clinical trial, melanoma patients vaccinated with gp100, an antigen found on the outside of melanoma tumor cells, produced immune cells that attacked their own cancer. Furthermore, tumors regressed in one-third of all metastatic melanoma patients who were given this vaccine in conjunction with interleukin 2 (IL-2), a molecule that helps boost the immune response. In pilot studies of vaccines developed from combinations of other melanoma-associated antigens, patients are experiencing substantial tumor regression, even without the help of IL-2 or other immune-boosting agents. In addition, transferring certain immune cells, such as

killer cells and other helper cells that will attack cancer antigens, back to the patient have produced additional tumor regressions. Scientists now are exploring molecular and genetic characteristics of breast, ovarian, prostate, and lung and colorectal cancers to identify antigens for vaccine development to combat these cancers.

Treatment vaccines for lung and colorectal cancers, the two most common cancers and the leading causes of cancer death in the United States, have been elusive. This year, NCI researchers developed a new two-step vaccine approach for lung and colorectal cancer treatment that produced promising results in an initial clinical trial. Researchers first created the vaccine material by isolating from tumor tissue a portion of carcinoembryonic antigen, a protein that is overexpressed in many cancers, including many of those that arise in the colon and lung. In the second step, they modified the protein to make it more potent, and then used an innovative delivery method that seems to heighten the immune response. Researchers hoped that the vaccinated patients would produce antibodies to attack the novel protein and consequently, the tumor cells that express it. After vaccination, tumors in two of 12 patients with lung or colon cancer dramatically regressed, one patient's response was mixed, and for the other two there was no change in their disease. These are promising findings for a Phase I trial, and if more extended clinical trials demonstrate its effectiveness, this approach could lead to a new vaccine therapy for lung, colorectal, and perhaps other cancers.

Boosting the Immune Actions of Blood-Producing Cells May Improve Breast Cancer Therapy
High-dose chemotherapy is often used to treat high-risk cases of breast cancer. Because this treatment kills not just tumor tissue, but also peripheral stem cells that are needed to produce new blood cells, some of these stem cells are harvested from the patient before their chemotherapy begins, and re-infused following treatment. This intensive therapy is not universally effective in eliminating tumors, however, and relapses are common. Researchers have been studying ways to make the treatment more effective using interleukin-2 (IL-2), a natural substance that boosts immune response by stimulating certain immune cells to reproduce, generating thousands of cells "armed" to fight the invader. Recently, in a Phase III study of 59 high-risk breast cancer patients, 30 patients were given back IL-2 treated stem cells after receiving high-dose chemotherapy. The other 29 patients received standard treatment. Toxicity levels were not different for the two groups and side effects were transient. Of the patients given IL-2-treated cells, 96 percent were surviving after two years, 76 percent cancer free. Of the patients given standard therapy, 76 percent were surviving, 51 percent cancer free. Incubating harvested blood-producing cells with IL-2 to stimulate them to attack breast cancer cells could significantly improve the efficacy of therapy for high-risk breast cancer, and improve longevity and quality of life for breast cancer survivors.

Immunotoxin Yields Promising Results Against Hairy Cell Leukemia in Early Trial
Every year, about 700 Americans are diagnosed with hairy cell leukemia (HCL), a rare, slow-growing cancer of white blood cells. HCL patients are usually treated with the chemotherapy drugs pentostatin or cladribine, and the majority of patients who receive these drugs experience complete remission and may remain disease-free for up to eight years. However, these chemotherapies can suppress infection-fighting white blood cells known as CD4 cells and at least 25 percent of treated patients develop drug resistance and respond poorly to other treatments. Researchers at the National Cancer Institute have developed a new immunotherapy

for HCL that works by using a specially designed molecule known as BL22 to deliver a deadly toxin directly to the leukemia cells. BL22 is made by joining portions of an endotoxin produced by the bacteria *Pseudomonas aeruginosa* with an antibody that recognizes and binds to CD22, a protein found on many leukemia cells, including those produced in HCL. Designed to reach a tumor target quickly and directly, BL22 binds to a cancer cell, delivers its poison and kills the cell. Its specificity for cancer cells keeps it from harming healthy cells, a common and clinically significant consequence of more traditional cancer therapies. Results show this innovative therapy to be the first treatment developed in more than 10 years to achieve complete remissions in the majority of HCL patients treated and the only treatment to achieve complete remissions in a majority of HCL patients in whom chemotherapy has been ineffective. These results are particularly impressive because they occurred in a Phase I trial, an early trial designed primarily to determine how to administer a drug safely, not cure the disease. If the results are confirmed in further trials, they offer new hope to HCL patients. It is also possible that BL22 will prove effective in treating other types of leukemia.

Molecular Profiles Help Identify Treatment Options

All cells have unique "molecular signatures," special characteristics such as specific genes that are active and proteins or other products manufactured by the cell. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and that change becomes a signal of the presence of cancer. In one application of this powerful new "molecular profiling" technology, investigators have begun to identify genetically distinct subsets of tumors that have different clinical courses. For example, NCI-funded scientists previously demonstrated that diffuse large B-cell lymphomas comprise two distinct subsets of tumors with significantly different outcomes. Now another group of NCI-supported investigators have identified two genetically distinct subsets of breast tumors that arise from two different types of breast cells, luminal and basal or basal-like. Tumors from luminal cells tested positive for estrogen receptors and those from basal cells tested negative. Past studies have revealed that patients with estrogen-receptor-positive breast tumors generally have better outcomes than patients whose tumors are estrogen-receptor-negative. Although further research is needed to correlate the tumor subsets with measurable clinical features of the disease, this study suggests that patients with basal cell-like breast tumors may benefit from early, aggressive therapy, while those with luminal cell-like tumors may be spared further treatment. These insights into molecular profiling hold the promise of improving how clinical decisions are made for individual patients. Classifying tumors based on molecular profiles will help oncologists select the most effective therapy for an individual and may help in the development of therapies that are targeted to specific subsets of tumors.

Scientists Identify Chemosensitive Gliomas

Gliomas are malignant tumors of the brain that arise from glial cells, those that provide support and insulation for neurons of the brain. Most gliomas are quickly fatal despite treatment, but the prognosis can vary depending on the type. Patients with oligodendroglioma, for example, respond well to combined treatment with the drugs procarbazine, lomustine, and vincristine, with approximately two-thirds experiencing long-term remissions. Only recently, however, have scientists learned how to identify which patients would respond to the combined treatment, based on the genetic mutations present in the glioma tissue. For example, patients with altered portions of chromosome 1 and 19 tend to respond much better to chemotherapy than those with mutations

in the genes *PTEN*, *EGFR*, and *CDKN2A*. These findings will improve the ability of physicians to recommend appropriate treatment for patients. Patients with responsive tumors will increase their chances of survival when they are treated quickly, while those with the remaining tumor types may be directed to alternative therapies.

Distinct Type of Pancreatic Cancer May Require Different Treatment
In recent years, scientists have begun to recognize that a specific type of pancreatic cancer, known as "medullary" cancer, is quite different from the conventional form of the disease. Medullary pancreatic cancer may represent 6 percent of all pancreatic cancers and affect thousands in the United States every year. NCI-funded investigators recently discovered that the genetic profile of medullary cancer is distinct from that of other pancreatic cancers, meaning that it will not necessarily respond to treatment in the same way as the typical form of pancreatic cancer. Consequently, it is important to identify patients with the medullary form of the disease as soon as possible after pancreatic cancer has been diagnosed. In addition, the researchers discovered that patients with medullary pancreatic cancer often have close relatives with breast, lung, colon, and other cancers, and may themselves be more susceptible to colorectal cancer and thus be candidates for genetic counseling and regular screening.

Reversing the Silence of a Gene May Make Cancer Therapy Effective
Neuroblastoma is the most common extracranial solid tumor occurring in children. Despite major advances in cancer chemotherapy and the use of bone marrow transplantation, the long-term survival rate for children with aggressive forms of the disease remains very low. One of the reasons for the poor prognosis has to do with its resistance to chemotherapeutic agents that work by inducing apoptosis (programmed cell death).[2] In the absence of this essential mechanism, cancer cells are able to rapidly multiply out of control. A group of NCI-supported researchers have begun to explore how neuroblastoma cells evade apoptosis. In a recent study, the scientists examined 18 human neuroblastoma cell lines and found that in 13, the gene responsible for producing caspase 8, a protein instrumental in inducing apoptosis, was inactivated or silenced by a DNA methylation process. The lack of the caspase 8 protein in these cells seemed to protect the cancer cells against a number of mechanisms that cause cell death, including, most importantly, chemotherapeutic agents that induce apoptosis in cancer cells by damaging their DNA. Reintroducing caspase 8 into neuroblastoma cells lacking the protein reversed apoptosis resistance. Researchers are now studying the possibility of using demethylation agents to reverse the chemical alteration that silences the caspase 8 gene, improving the susceptibility of neuroblastoma cells to a variety of chemotherapies.

NEW INITIATIVES

NCI will move forward with a large number of new and expanded initiatives in Fiscal Year 2003. These activities will respond to a wide range of research areas, identified by members of the cancer research and advocacy community. Progress Review Groups have made recommendations for cancer site-specific research and numerous other experts have provided

[2] Apoptosis is a normal biological process in which damaged or unneeded cells undergo a cascade of self-induced events leading to their destruction and absorption by the body.

input to broad-based scientific priorities such as the exploration of molecular signatures and imaging technology, public health concerns such as cancer-related health disparities, and infrastructure needs such as those described for clinical trials. All will help address the many unanswered questions about who gets cancer, when, and why.

Cancer Prevention and Control Studies

Selenium and Vitamin E Cancer Prevention Trial
The Selenium and Vitamin E Cancer Prevention Trial, the largest-ever prostate cancer prevention study, will be the first to look specifically at the effects of these two dietary supplements in preventing prostate cancer. NCI will be conducting this trial in partnership with the Southwest Oncology Group, one of several clinical trials cooperative groups sponsored by the Institute. This 12-year study will follow more than 32,000 men recruited through more than 400 sites in the United States, Puerto Rico, and Canada. After skin cancer, prostate cancer is the second most common form of cancer in men.

Expanded Research on Tobacco and Tobacco-Related Cancers
NCI will expand efforts to define the biological, behavioral, and social bases of tobacco use and addiction; support clinical and population studies on the interplay among tobacco, other exposures such as alcohol and asbestos, and susceptibility to cancer risk; promote the integration of biospecimen collection into screening trials to better understand the molecular basis of early-stage lung cancer; and facilitate scientific collaborations between investigators studying lung and head and neck cancer through Specialized Programs of Research Excellence and investigators at Transdisciplinary Tobacco Use Research Centers to better integrate biological, pharmacological, and behavioral research on tobacco use and its impact on disease. These activities will help address the concerns of the many scientists and advocates who have provided input to research needs associated with lung cancer – through the Lung Cancer Progress Review Group – and other cancers linked to tobacco use.

Tobacco Intervention Research Program
NCI will establish the Tobacco Intervention Research Program, a state-of-the-science center for tobacco use research by intramural and extramural scientists conducting genetic, epidemiological, basic science, and behavioral research studies related to the treatment of nicotine dependence. The program is expected to start with one to two research projects in fiscal year 2003, including a study comparing the efficacy of all FDA-approved medications for smoking cessation.

Early Detection and Diagnosis Trials

National Lung Screening Trial
The National Lung Screening Trial (NLST) will endeavor to answer the controversy over benefits of screening and early detection tests for lung cancer. Enrolling some 50,000 participants in all, the trial will be used to determine (1) if lung cancer mortality is reduced in long-term current and former smokers by screening with spiral computed tomography (CT) as compared to chest x-ray and (2) what the risk/benefit ratio is for these tests. Participants will be long-term smokers aged 55 to 74 who have not been diagnosed with lung or other cancers.

Investigators will also the measure sensitivity, specificity, predictive value, nodule management, and cost-effectiveness of spiral CT, as well as quality of life and biomarkers. The trial will build on the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the Lung Screening Study and will be carried out through a collaboration between NCI (80%) and the American College of Radiology Imaging Network (20%).

Digital Mammographic Imaging Screening Trial
Through one of its clinical trials cooperative groups, the American College of Radiology Imaging Network, the NCI will launch the Digital Mammographic Imaging Screening Trial. This multi-year trial will involve nearly 50,000 women from the United States and Canada and will be the first large, multicenter study to compare digital to standard mammography. This study should determine whether the higher resolution imaging of digital mammography can detect breast cancer more accurately than standard mammography.

Better Cancer Treatments

Molecular Targets Laboratories
Molecular Targets Laboratories funded by the National Cancer Institute will capitalize on the opportunities emerging from genomics, molecular biology, combinatorial chemistry, informatics, and imaging to create a resource of biological assays and chemical probes to allow investigators to easily identify and test cancer-related targets for drug discovery. This work enables biological studies of cancers as well as prevention and treatment drug discovery.

Clinical Proteomics Program
NCI will continue to expand the Clinical Proteomics Program, working in partnership with the Food and Drug Administration. Proteomics is the systematic study of protein expression and function and is an important next phase in our pursuit of molecular medicine. In cancer, alterations in genes can cause defects in the corresponding proteins, the functional machinery of the cell. This protein damage disrupts the normal communication networks of the cell in a way that leads to malignancy. Using proteomics, cancer researchers are learning how disruptions in the protein communication networks drive the growth and spread of cancer and are applying this knowledge to early detection, prevention, and drug development.

Radiation Modifier Evaluation Module Program
The Radiation Modifier Evaluation Module (RAMEM) program will serve intramural investigators and industry in the design and development of treatments using novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Integrating molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy is a high priority of the National Cancer Institute's Intramural Program.

Expansion of Other Drug Discovery Programs
NCI will also expand support for the National Cooperative Drug Discovery Groups, expand the availability of NCI drug discovery resources to academic laboratories through the Rapid Access to NCI Discovery Resources program, expand efforts to collect, inventory, and distribute diverse compounds - synthetic chemicals, natural products, and biological materials, and provide informatics support for anti-cancer research.

Understanding the Causes of Cancer

Study of Genetic and Environmental Exposure Interactions
NCI Cohort Consortium investigators will combine data from a number of prospective cohort studies to uncover potential interactions between established environmental risk factors and genetic variants for breast and prostate cancer. This collaboration will compile over 7,000 cases of each cancer to maximize statistical power and allow rapid assessment of the consistency of findings across studies. This study will serve as a model for future efforts that can take full advantage of investments in large population studies to advance cancer research and care.

Collaborative Studies of High-Risk Individuals
NCI will support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility. Funds will be used to sustain the Cancer Genetics Network as a resource for studies of clinical care for early detection, diagnosis, and treatment of genetically high-risk individuals, including those from minority and underserved populations; expand support for studies in cancer genetics that examine psychosocial responses to cancer risk communication within average and high-risk populations in order to inform the development of effective educational strategies and resources for patients, providers, and the public; and continue to support research in cancer survivorship to evaluate physiologic and/or psychosocial effects of cancer or its treatment among survivors of cancer, and examine the role of genetic factors in these impacts. NCI will also collaborate with the Centers for Disease Control and Prevention's Genomics and Public Health Centers to develop methodological standards specific to the collection and reporting of data from NCI consortia on gene-environment interactions, effectively relating these results to medical practice and public health.

Intervention Research for Reducing Cancer-Related Health Disparities

Southern Community Cohort Study
NCI recently launched the Southern Community Cohort Study to determine why African Americans have higher rates of most forms of cancer and are more likely to die from cancer than Whites, Asian/Pacific Islanders, American Indians, or Hispanics. Enrolling 105,000 people, two-thirds of whom will be African Americans, this will be the first study of its kind in the southern United States and the largest-ever population-based health study of African Americans. It is expected that the evidence gathered in the course of this study will help develop prevention strategies to lower the rates of cancer among all ethnic groups.

Centers for Population Health and Cancer
The new Centers for Population Health and Cancer will be the research keystone of NCI's efforts to reduce cancer health disparities. Using an interdisciplinary and integrated research team approach, these Centers will conduct studies focused on understanding the causes of health disparities in cancer and developing effective interventions to reduce them. Each Center will support at least three cancer control and population research projects exploring the social factors in cancer and how they interact with behavioral and biological pathways. They also will provide

funding for training, pilot projects, and shared resources. Each must implement strategies to enable extensive collaboration.

Continuing Umbrella of Research Experiences Program
NCI will expand the Continuing Umbrella of Research Experiences Program to substantially increase the number of trainee positions for minority researchers in both basic research and clinical oncology; provide new supplemental funding to cancer centers for high school and undergraduate student research experience; and fund new Minority Investigator Supplements to NCI research project grants and new Career Transition Awards for basic, clinical, behavioral, and population minority scientists in their first junior faculty positions.

Collaborations and Translational Research

Activities to Promote Research Collaborations Program
Recognizing the multi-disciplinary nature of cancer research and the critical need to encourage collaborative research, NCI will expand supplemental funding to grants for the promotion of new interdisciplinary collaborations through initiatives such as the Activities to Promote Research Collaborations Program.

Centers of Research Excellence
NCI will continue to expand several centers of research excellence to more comprehensively address needs for translational research. A prime example will be the expansion of Specialized Programs of Research Excellence (SPOREs). The existing 27 SPOREs focus on research for breast, lung, gastrointestinal (including pancreatic), ovarian, prostate, genitourinary, and skin cancer. NCI will expand the program in 2003 by adding three new SPOREs in pancreatic cancer, one in genitourinary cancer, one in lung cancer, two in leukemia, one in myeloma, one in ovarian cancer, one in prostate cancer, and one in skin cancer. NCI also plans to support development of an Internet platform and research database to exchange research results and to foster communications for sharing resources and developing collaborative inter-SPORE research projects and provide supplemental funding to SPOREs for planning and developing inter-SPORE research projects.

NCI Center for Bioinformatics
NCI will expand its backbone informatics infrastructure to support and integrate basic, clinical, translational, and population research initiatives. These efforts will facilitate information exchange within and between NCI-supported research initiatives and support bench-to-bedside information integration and use.

Accelerating the Pace of Cancer Clinical Trials

NCI plans to increase funding to ensure substantially greater physician and patient participation in clinical trials. Funds will be used to shorten the length of time it takes to accrue patients to important national trials, increase the reimbursement to $3,500 per patient for treatment and prevention trials to adequately cover the additional nursing and data management costs required to participate in clinical trials, double the number of patients accrued to treatment and prevention

trials over 1 to 2 years, and provide follow-up funding to allow physicians to follow patients and report outcome data for many years and address important long-term treatment and epidemiology issues. NCI also expects to expand the Clinical Trials Support Unit to consolidate the administrative tasks associated with clinical trials and to provide a single interface for investigators enrolling patients, provide extensive information about prevention and treatment options and clinical trials to enable patients and physicians to make informed medical choices, and facilitate clinical trials participation by developing uniform electronic case report forms and data reporting systems.

Expanding Research Resources

Genetic Analysis
NCI will also initiate a Cancer Molecular Analysis Project to more fully integrate molecular signatures, targets, and interventions; extend the Genetic Annotation Initiative to identify new cancer related gene polymorphisms in defined populations; define key molecular pathways by thoroughly characterizing the impact of genetic variations on numerous gene and protein expression profiles; and develop human gene expression profiles from specific tissues with measured exposure times to study epigenetic effects and cell pathways that lead to tumor formation.

Shared Pathology Informatics Network
The Shared Pathology Informatics Network, a consortium of institutions connected by a model Web-based system, will improve scientists' access to human specimens and relevant clinical data. The system will automatically access information from medical databases and respond to queries by identifying, obtaining, and returning data for specimens that meet the defined search criteria, after removing information that could compromise patient privacy.

Microarrays
The Tissue Array Research Program (TARP), which stemmed from collaboration among NCI and the National Human Genome Research Institute scientists, will continue to support the development of multi-tumor, tissue screening microarray slides. The slides contain up to 600 tissue core samples from different tumor tissues as well as normal tissue and specific cell lines grown in the laboratory. Researchers use the slides for high-throughput, comprehensive analysis of the molecular profile of each tumor type represented on the slide. With approximately 11,000 array slides already distributed to researchers nationwide, TARP plans to scale up production and to increase dissemination of this technology to interested scientific investigators.

OTHER AREAS OF INTEREST

In recent years, NCI's research portfolio has increasingly emphasized technology research and development, vital tissue resources, targeted drug development and clinical trials, and the quality of cancer care. Today, this research is more likely than ever before to be carried out by multidisciplinary teams of scientists, working in NCI-sponsored networks and consortia or in its newly restructured intramural program. And NCI's work does not end with research but extends into the dissemination of research findings.

Defining the Molecular Signatures of Cancer Cells
The Innovative Molecular Analysis Technologies (IMAT) Program supports the development and application of new technologies for identifying molecular changes that distinguish cancer cells from normal cells. The IMAT Program has supported nearly 140 research projects, and includes areas of technology development that have not traditionally received NCI support, such as spectrometry analysis, integrated microscopy, and software development.

The Early Detection Research Network (EDRN) is aimed at the discovery and development of novel biomarkers for all cancers and for precancerous lesions. Separate EDRN laboratories cooperate to streamline the development, validation, and clinical testing of promising molecular signatures of cancer for use as biomarkers for cancer screening and early detection. To date, EDRN researchers have discovered biomarkers for the early detection of several types of cancers, including breast, esophageal, and prostate.

Molecular Targets for Prevention and Treatment
The Interdisciplinary Research Teams for Molecular Target Assessment are sponsored by a new program that enables interdisciplinary teams of scientists to develop molecular assays, molecular and cellular imaging probes, and other tools to assess the effects of targeted interventions in preclinical models and in early clinical trials. The teams will study critical biological processes to uncover high-priority targets for cancer prevention or treatment and drug discovery.

The Biology-Chemistry Centers conduct research with an emphasis on new technologies for cancer drug discovery. Multidisciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of chemically diverse structures with potential anti-cancer effects. Using "smart " assays, scientists screen the compounds to identify those that will interact with cancer-specific molecular targets. The six teams funded to date have screened hundreds of thousands of compounds for anti-cancer activity.

Cancer Imaging
NCI's Development of Novel Imaging Technologies program stimulates: (1) the development of highly innovative image acquisition and enhancement methods, including high risk/high gain projects that exploit our expanding knowledge of the molecular basis of cancer and other diseases and (2) the integration of these emerging technologies with traditional imaging modalities. Investment in these innovations will enable scientists to identify and characterize the molecular changes that occur both during early cancer formation and in response to intervention or therapy.

The Development of Clinical Imaging Drugs and Enhancers (DCIDE) program fosters the development of new imaging contrast agents and molecular probes to improve the diagnosis and treatment of cancer. In the first year of DCIDE, two agents were selected for further development: one new contrast agent for positron emission tomography (PET) imaging of prostate and other cancers, and one new probe for magnetic resonance imaging of early blood vessel formation that accompanies tumor development.

NCI's *In vivo* Cellular and Molecular Imaging Centers bring together experts such as biomedical engineers, cellular and molecular biologists, pharmacologists, and imaging scientists to conduct

multidisciplinary research on cellular and molecular imaging. The technologies developed should improve our ability to prevent, detect and diagnose, and treat cancer.

Cancer Clinical Trials

NCI is increasing collaborations between clinical trials and laboratory studies, with over half of the trials initiated by NCI's cooperative groups in the last two years including laboratory collaborations. In the last decade, a vast array of new molecular targets have been identified for possible use in cancer treatment and prevention interventions and new technologies are being developed to test for these targets in patients. Clinical trials of target agents depend on laboratory studies to better define the presence of these targets, which involve complex cellular interactions, and the effect of drugs designed to "hit" these targets in patients. Similarly, clinical trials for chemopreventative agents increasingly are including correlative laboratory studies.

NCI's netTrials™ provides intramural investigators with a Web-based clinical trials information system that streamlines operations and improves data quality, patient safety monitoring, and analysis of much larger groups of data across the entire clinical trials portfolio. Still under development, netTrials™ is being used by at least six clinical branches of NCI's Center for Cancer Research. Plans include expanding it to include all intramural clinical studies.

The Cancer Trials Support Unit allows extramural clinical investigators to access clinical trial protocols and other information, enroll patients in clinical trials online, arrange for reimbursement of research costs, and receive alerts when new trials begin. This system of business support tools has eliminated redundancy, reduced the administrative burden on researchers, and dramatically enhanced program efficiency.

Through its Special Populations Networks (SPNs) for Cancer Awareness Research and Training and in collaboration with Minority-Serving Institutions, NCI is working to increase access to and involvement in clinical trials by minority researchers, patients, and physicians.

Quality of Cancer Care

The NCI is collaborating with the National Institute of Nursing Research and five other NIH Institutes and Centers to generate scientific knowledge to improve the Quality of Life for Individuals at the End of Life. The project includes clinical or care delivery studies focused on management of physical and psychological symptoms, patient-provider and patient-family communication, ethics and clinical decisionmaking, caregiver support, or the context of care delivery for those facing life-limiting illnesses.

The Cancer Care Outcomes Research and Surveillance Consortium will support prospective cohort studies on more than 10,000 patients with newly diagnosed lung or colorectal cancers. The project is designed to (1) elucidate the relationship between cancer care practices in the general population and patient outcomes, including survival and quality of life, and (2) assess community practice patterns and disparities in care between population subgroups.

Dissemination of Research Findings

NCI has put in place a number of mechanisms to assist scientists in the dissemination of research findings. For example, the Cancer Intervention and Surveillance Modeling Network supports the

use of modeling to study the impact of interventions on cancer trends at state, local, and national levels. This modeling is used to explore incidence and mortality trends, predict the impact and analyze the effectiveness of interventions, and study optimal control strategies.

In addition, the Program for the Assessment of Clinical Cancer Tests (PACCT) facilitates the translation of new knowledge about cancer and new technologies to clinical practice. For example, PACCT supports the generation of reference sets of clinical specimens, which will be made available to researchers in academics and industry who evaluate new markers and validate the utility of some known makers and tests. This program is also supporting the development of criteria to help determine the data needed to move a marker test forward to clinical practice.

Other mechanisms for assisting with dissemination of research findings include strengthening partnerships with voluntary health organizations, HMOs, and community organizations; funding competitive supplements to NCI grantees who have effective cancer control interventions ready for dissemination; and convening, in collaboration with private organizations and other Federal agencies, an interdisciplinary group to develop recommendations for intervention researchers.

INNOVATIONS IN MANAGEMENT AND ADMINISTRATION

Managing for Results in NCI's Business and Administrative Units
Each NCI business and administrative unit is developing a 4-year strategic plan to assure that it is prepared to provide the results its customers need, when they need them. As part of the planning process, each unit is identifying its measurable, mission-critical goals, strategies for achieving those goals, measures to assess progress toward goal achievement, and potential barriers to success and strategies to overcome them. Units will self-evaluate annually. In addition, NCI has designed and tested a process for conducting external reviews of each business and administrative unit every 4 years. Follow-up survey results suggest that the review process will provide valuable insight into ways to improve NCI operations. NCI will share the plans with other Federal agencies along with the guidelines for NCI's new external review process.

Information Technology: Network Services and Training Program
NCI continues to enhance information technology services to both scientific and management staff. We are working to address the considerable data storage needs of researchers, especially those working in the areas of genetics and imaging and other areas that demand significant information resources. We currently store more than three terabytes of scientific data. Accompanying this increase in data storage is the implementation of security and performance enhancements for Web sites and network operations. We have implemented the Rational Unified Process for development projects. This industry standard approach is designed to decrease risk and improve software product quality.

Technology Transfer
NCI is committed to forging scientific collaborations with the private sector and academia to help accelerate the pace of cancer research and ensure that Federally developed technologies reach the public in the form of new drugs and diagnostics as quickly as possible. NCI has established outreach initiatives to promote collaborative research and to educate scientists about the full scope of partnership possibilities available through NCI. In April 2001, NCI hosted a

forum which brought together scientists from industry and NIH to discuss the most recent innovations in research and to identify collaborative research opportunities. NCI has also established Web sites that list collaborative research opportunities and the agreements used to facilitate the collaborations.

Academy for Career Excellence
Currently under development, the NCI's Academy for Career Excellence will create an NCI-wide competency-based educational program that (1) provides standardized courses to specific categories of employees; (2) addresses scientific and administrative training needs; (3) recognizes staff training efforts; and (4) reinforces compliance with delegations of authority. Features will include formal curricula, existing and newly created courses, a Web-based course catalog, and a variety of training venues. The objective is to support workers in maximizing their knowledge as well as to retrain the workforce where necessary to keep up with changing technologies and work requirements.

STORY OF DISCOVERY
Making the Connections for a Targeted Cancer Treatment Takes Time and Perseverance

May 10, 2001 marked an important milestone in the fight against cancer. News outlets all over the country announced that a promising drug called Gleevec™ had been approved to treat a serious blood cancer known as chronic myelogenous leukemia (CML). The drug is one of the first of its kind to be approved – a targeted agent that hones in on specific molecules in cancer cells, leaving healthy cells unharmed. But the development of Gleevec™ is far from an overnight breakthrough. The road to its discovery was paved through knowledge culled from more than 40 years of studies – many of which were funded by the National Cancer Institute – probing the molecular events associated with cancer development, the use of new technologies that enabled scientists to move in directions previously beyond reach, and quite often, unanticipated opportunity. The story involves recognizing the unique chromosomal abnormalities of CML, identifying the related cancer-causing protein, finding a treatment agent that targets that protein, and testing and proving its effectiveness and readiness for use in treating cancer.

The Philadelphia Chromosome: Uncovering the Fundamental Nature of CMLThe story really began in 1960 when Drs. Peter Nowell and David Hungerford, two Philadelphia-based physicians, made a curious discovery. They noticed that cells from CML patients were missing a short segment on one member of the 22nd pair of chromosomes. This shortened chromosome became known as the "Philadelphia chromosome." It was the first chromosome abnormality ever found to be associated with a specific cancer and the first indication that tumors might indeed arise from changes beginning in just one cell. While the link between the Philadelphia chromosome and CML led scientists to suspect a causal relationship, the location of the missing DNA from chromosome 22 and how it might lead to CML was a mystery to be solved over the next three decades.

In the early 1970s, new staining techniques offered a way to more precisely visualize chromosome band patterns – characteristic markings that can be used to identify individual chromosomes. With this technique, Dr. Janet Rowley determined that chromosome 9 in CML patients was lengthened by the same amount that chromosome 22 was shortened. From this observation, Rowley proposed that the genetic material from the two chromosomes was reciprocally exchanged, or "translocated."

Using newly developed approaches for molecular analysis, scientists in the early 1980s determined that the genetic rearrangement that leads to the Philadelphia chromosome occurs when genetic mistakes cause breaks in the middle of two vital genes located on chromosomes 9 and 22. They found that the break on chromosome 22 occurs in the middle of the *bcr* gene and that the break on chromosome 9 occurs in the *abl* gene. On the shortened end of chromosome 22, the genetic rearrangement produces the abnormal *bcr-abl* gene, the source of CML development.

In 1986, Dr. David Baltimore and his research group determined that, like the normal *abl* gene, the defective *bcr-abl* gene carries the code for a tyrosine kinase, a class of proteins that plays an important role in regulating cell growth

and division. The normal *abl* gene will turn on or off, producing tyrosine kinase to promote cell growth as needed. The aberrant *bcr-abl* gene, however, is always turned on and lacks the critical piece that enables the gene to turn itself off. As a consequence, *bcr-abl* floods the cell with the instruction to divide constantly and also prevents the leukemia cells from undergoing normal programmed cell death or apoptosis, a process that helps to regulate white blood cell numbers. Several laboratories confirmed the link between the defective gene and CML through studies showing that the *bcr-abl* gene was all that was needed to induce leukemia in mice.

Developing a Targeted Treatment

During this same time period, advances in molecular biology were revolutionizing the field of drug discovery. In the laboratories of Swiss pharmaceutical company Ciba-Geigy (later, Novartis), scientists were able to apply unfolding knowledge about the workings of cellular pathways and communications systems in a number of drug development efforts. In one research program, scientists were looking for agents to inhibit protein kinases – a group of cell signaling proteins that includes the Abl protein. A number of such agents were found, including one that they labeled STI571.

Meanwhile, American oncologist Dr. Brian Druker was interested in determining how the Bcr-Abl protein, the product of the *bcr-abl* gene, fits into the complicated circuitry of cell signaling. His research led him to believe that the Bcr-Abl protein could be a powerful target for a drug that could impede the activity of the protein and be an effective treatment for CML. When he learned about Ciba-Geigy's complementary research, Druker asked scientists there for candidate protein kinase inhibitors that he could test against leukemia cells. At the end of 1993, the pharmaceutical company sent him several candidates, including STI571. Druker screened the chemicals and found that STI571 halted the growth of the leukemia cells but had little effect on healthy ones.

While this was an exciting outcome, there were still many obstacles to overcome. The process of developing a new drug and getting it approved for use is lengthy and expensive. Scientists must identify a possible agent; study and test it for efficacy, pharmacology, and toxicology; file with the Food and Drug Administration; and finally evaluate it through clinical trials. STI571 posed an additional business problem because the incidence of CML is quite low, limiting the potential demand for the drug, and two moderately effective treatments already were available for CML, although both held potential for serious side effects.

Despite reservations, Novartis agreed to produce enough STI571 for an initial clinical trial. Dr. Druker began the Phase I trial, conducted to identify a safe dose level, in June of 1998. By December of 1999, he and his colleagues reported that white blood cell counts for all of the 31 patients receiving a high dose of STI571 had returned to normal, an effect that was sustained for the 8 months that the patients stayed on the drug. In 9 of the 20 patients who were treated for 5 months or longer, no leukemia cells could be found, confirming that the drug was eliminating the source of the cancer. In addition to these remarkable results, the drug had minimal side effects.

Rarely are such dramatic results seen in a Phase I trial. As the news spread, more and more CML patients began to request the treatment.

In response to these exciting findings, Druker and his colleagues conducted a larger study and reported in April 2001 that STI571 restored normal blood counts in 53 of 54 CML patients, all of whom had resisted previous chemotherapy. Of these patients, 51 were still doing well after a year on the medicine, with most reporting few side effects. Following "fast-track" review, the Food and Drug Administration approved STI571, now known as Gleevec™, as a treatment for CML in May 2001, beginning with patients not responding to standard therapies.

The Story Continues

Patients receiving Gleevec™ as a treatment for CML need to be followed for longer periods to determine whether the positive effects will last and whether long-term treatment can cause side effects. Unfortunately, most patients with advanced disease relapse within a year. The cause of resistance is now known, so scientists are trying to overcome it. Like most successful treatments, Gleevec™ will undoubtedly spawn a host of refinements.

In addition to the Bcr-Abl signaling protein, the drug appears to target two other protein kinases, the c-kit receptor and the PDGF receptor. The c-kit receptor is active in gastrointestinal stromal tumor (GIST), a cancer that affects connective tissue in the digestive system. The PDGF receptor is associated with many types of cancer, one of which

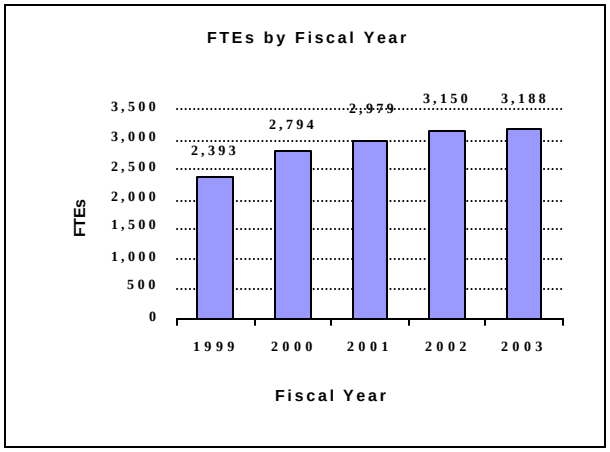
is a form of brain cancer called glioblastoma. Cancers of the breast, ovary, and lung may also be effectively treated with Gleevec™. Both NCI-supported and private-sector scientists are currently conducting a number of different clinical trials to determine the effectiveness of Gleevec™ against these other cancers.

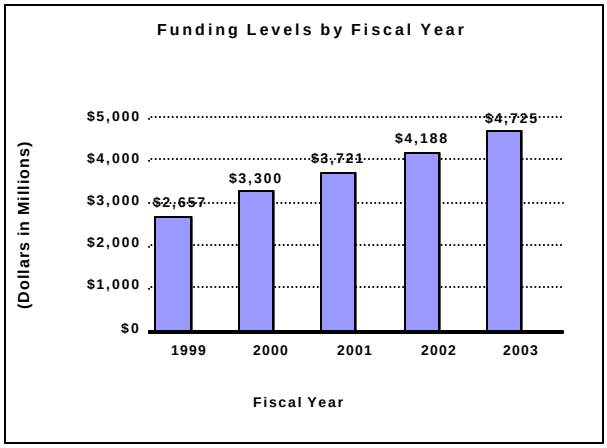
The success of Gleevec™ offers substantial hope that molecular targeting is a highly effective strategy in the fight against cancer, provided that the target is carefully chosen and validated. As scientists identify additional cellular mechanisms that drive tumor growth, it will be possible to design tailor-made agents that selectively take aim at these targets to thwart the growth of specific cancers. It is likely that Gleevec™ is the first of many potent, but safer, targeted preventive and treatment drugs to be developed as a result of advances in understanding cancer at the molecular level.

Budget Policy

The Fiscal Year 2003 budget request for the NCI is $4,724,505,000, including AIDS, an increase of $514,784,000 and 12.2 percent over the FY 2002 level.

A 5 year history of FTEs and funding levels for NCI are shown in the graphs below. Note that Fiscal Years 2000 and 1999 are not comparable for the Managerial Flexibility Act of 2001 legislative proposal.



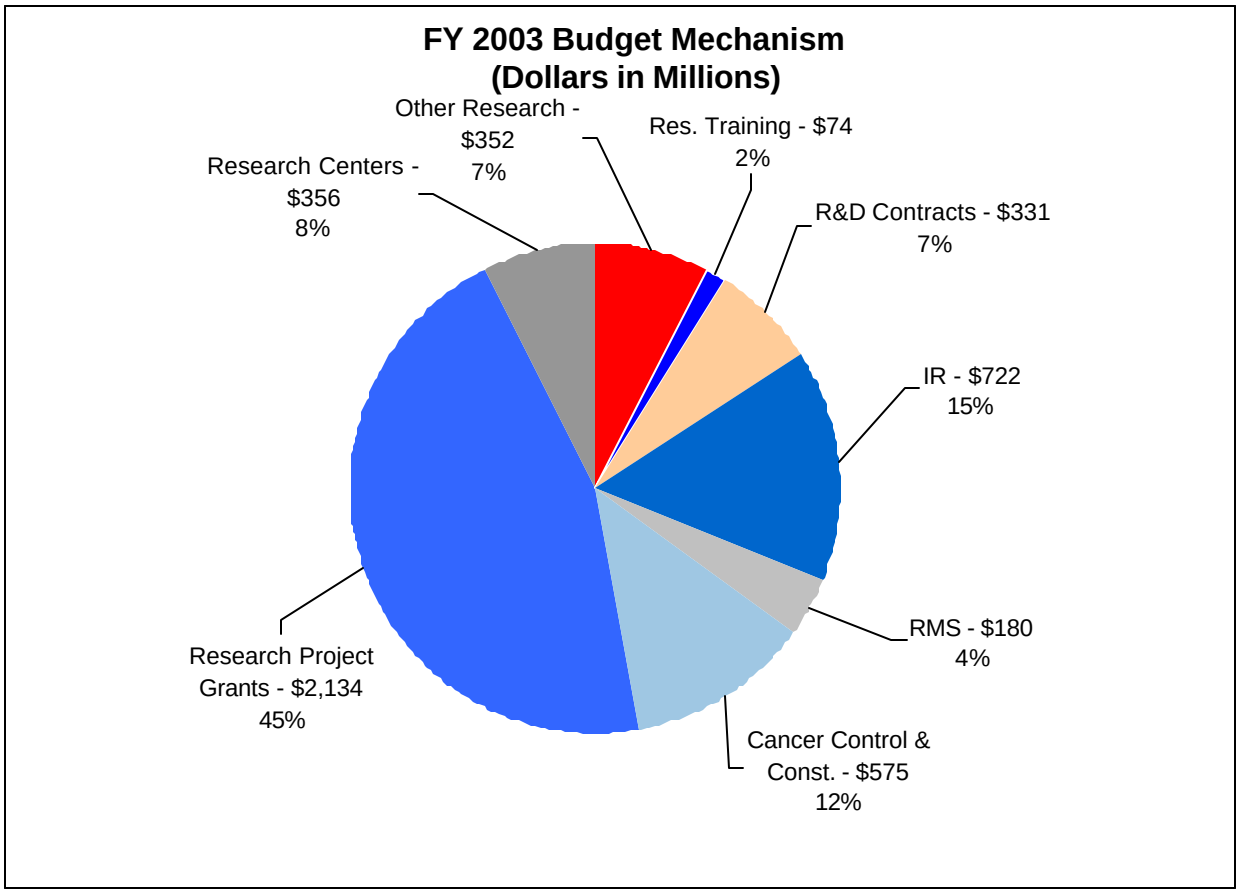


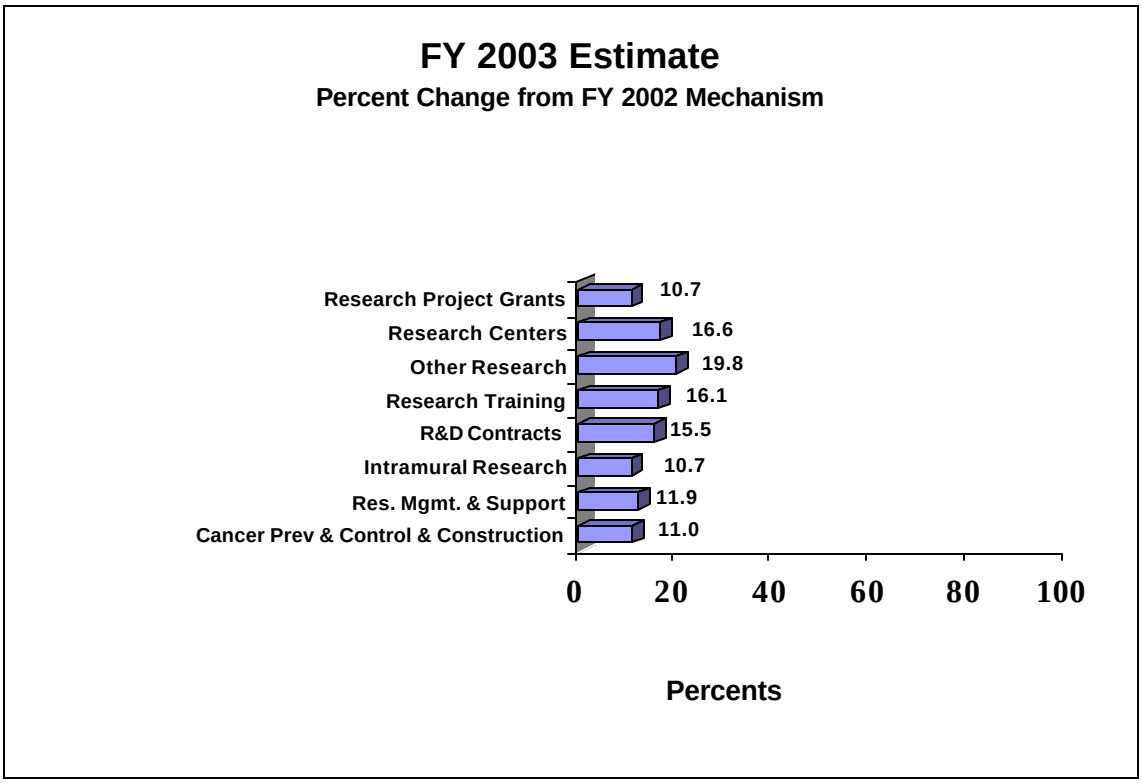
One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2003 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4 percent. Noncompeting RPGs will be funded at committed levels which include increases of 3 percent on average for recurring direct costs.

Future promises for advancement in medical research rest in part with new investigators with new ideas. In the Fiscal Year 2003 request, NCI will support 1,787 pre- and postdoctoral trainees in full-time training positions, an increase of 195 over FY 2002. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2002 levels.

The Fiscal Year 2003 request includes funding for 110 research centers, 850 other research grants, including 406 research career awards, and 151 R&D contracts. The R&D contracts mechanism also includes support for 82 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs. Intramural Research and Research Management and Support receive increases of 10.7 percent and 11.9%, respectively, over FY 2002.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
TOTAL - Current Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	3190	$1,157,843,000	3409	$1,351,657,000	3409	$1,351,657,000	3441	$1,462,799,000
Administrative supplements	(392)	36,831,000	(330)	34,822,000	(330)	34,822,000	(375)	44,679,000
Competing:								
Renewal	319	150,688,000	345	157,779,000	345	157,779,000	367	190,073,000
New	848	264,576,000	851	286,424,000	851	286,424,000	983	333,473,000
Supplements	5	750,000	26	10,900,000	26	10,900,000	5	1,200,000
Subtotal, competing	1172	416,014,000	1222	455,103,000	1222	455,103,000	1355	524,746,000
Subtotal, RPGs	4362	1,610,688,000	4631	1,841,582,000	4631	1,841,582,000	4796	2,032,224,000
SBIR/STTR	311	71,633,000	315	86,361,000	315	86,361,000	357	101,361,000
Subtotal, RPGs	4673	1,682,321,000	4946	1,927,943,000	4946	1,927,943,000	5153	2,133,585,000
Research Centers:								
Specialized/comprehensive	93	279,731,000	104	305,076,000	104	305,076,000	110	355,808,000
Clinical research	0	0	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0	0	0
Research Centers in Minority Institutio	0	0	0	0	0	0	0	0
Subtotal, Centers	93	279,731,000	104	305,076,000	104	305,076,000	110	355,808,000
Other Research:								
Research careers	358	51,177,000	358	54,177,000	358	54,177,000	406	65,327,000
Cancer education	91	21,740,000	89	22,400,000	89	22,400,000	93	25,206,000
Cooperative clinical research	138	154,261,000	138	168,108,000	138	168,108,000	153	198,060,000
Biomedical research support	0	0	0	0	0	0	0	0
Minority biomedical research support	0	3,479,000	0	3,979,000	0	3,979,000	0	4,522,000
Other	146	38,161,000	168	45,193,000	168	45,193,000	198	58,886,000
Subtotal, Other Research	733	268,818,000	753	293,857,000	753	293,857,000	850	352,001,000
Total Research Grants	5499	2,230,870,000	5803	2,526,876,000	5803	2,526,876,000	6113	2,841,394,000
Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards	180	6,583,000	180	7,283,000	180	7,283,000	204	8,545,000
Institutional awards	1412	51,344,000	1412	56,800,000	1412	56,800,000	1583	65,845,000
Total, Training	1592	57,927,000	1592	64,083,000	1592	64,083,000	1787	74,390,000
Research & development contracts	131	265,824,000	137	288,006,000	136	286,979,000	151	331,471,000
(SBIR/STTR)	(5)	(2,097,000)	(5)	(2,197,000)	(5)	(2,197,000)	(5)	(2,276,000)
	FTEs		FTEs		FTEs		FTEs	
Intramural research	1,884	567,297,000	1,991	639,719,000	1,991	638,692,000	2,015	708,299,000
Research management and support	771	136,509,000	815	154,904,000	815	154,904,000	825	173,781,000
Cancer prevention & control	324	459,482,000	344	511,817,000	344	511,817,000	348	568,059,000
Construction		3,000,000		5,000,000		5,000,000		5,000,000
Total, NCI	2,979	3,720,909,000	3,150	4,190,405,000	3,150	4,188,351,000	3,188	4,702,394,000
(Clinical Trials)		(648,622,000)		(701,000,000)		(701,000,000)		(785,300,000)

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
TOTAL - Accrued Costs for Retirement and Health Benefits
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting								
Administrative supplements								
Competing:								
Renewal								
New								
Supplements								
Subtotal, competing								
Subtotal, RPGs								
SBIR/STTR								
Subtotal, RPGs								
Research Centers:								
Specialized/comprehensive								
Clinical research								
Biotechnology								
Comparative medicine								
Research Centers in Minority Institutions								
Subtotal, Centers								
Other Research:								
Research careers								
Cancer education								
Cooperative clinical research								
Biomedical research support								
Minority biomedical research support								
Other								
Subtotal, Other Research								
Total Research Grants								
Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards								
Institutional awards								
Total, Training								
Research & development contracts (SBIR/STTR)								
	FTEs		FTEs		FTEs		FTEs	
Intramural research		$12,154,000		$13,507,000		$13,507,000		$13,975,000
Research management and support		4,974,000		5,529,000		5,529,000		5,722,000
Cancer prevention & control		2,090,000		2,334,000		2,334,000		2,414,000
Construction								
Total, NCI	0	19,218,000	0	21,370,000	0	21,370,000	0	22,111,000
(Clinical Trials)		(0)		(0)		(0)		(0)

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
TOTAL - Proposed Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	3190	$1,157,843,000	3409	$1,351,657,000	3409	$1,351,657,000	3441	$1,462,799,000
Administrative supplements	(392)	36,831,000	(330)	34,822,000	(330)	34,822,000	(375)	44,679,000
Competing:								
Renewal	319	150,688,000	345	157,779,000	345	157,779,000	367	190,073,000
New	848	264,576,000	851	286,424,000	851	286,424,000	983	333,473,000
Supplements	5	750,000	26	10,900,000	26	10,900,000	5	1,200,000
Subtotal, competing	1172	416,014,000	1222	455,103,000	1222	455,103,000	1355	524,746,000
Subtotal, RPGs	4362	1,610,688,000	4631	1,841,582,000	4631	1,841,582,000	4796	2,032,224,000
SBIR/STTR	311	71,633,000	315	86,361,000	315	86,361,000	357	101,361,000
Subtotal, RPGs	4673	1,682,321,000	4946	1,927,943,000	4946	1,927,943,000	5153	2,133,585,000
Research Centers:								
Specialized/comprehensive	93	279,731,000	104	305,076,000	104	305,076,000	110	355,808,000
Clinical research	0	0	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0	0	0
Research Centers in Minority Institutio	0	0	0	0	0	0	0	0
Subtotal, Centers	93	279,731,000	104	305,076,000	104	305,076,000	110	355,808,000
Other Research:								
Research careers	358	51,177,000	358	54,177,000	358	54,177,000	406	65,327,000
Cancer education	91	21,740,000	89	22,400,000	89	22,400,000	93	25,206,000
Cooperative clinical research	138	154,261,000	138	168,108,000	138	168,108,000	153	198,060,000
Biomedical research support	0	0	0	0	0	0	0	0
Minority biomedical research support	0	3,479,000	0	3,979,000	0	3,979,000	0	4,522,000
Other	146	38,161,000	168	45,193,000	168	45,193,000	198	58,886,000
Subtotal, Other Research	733	268,818,000	753	293,857,000	753	293,857,000	850	352,001,000
Total Research Grants	5499	2,230,870,000	5803	2,526,876,000	5803	2,526,876,000	6113	2,841,394,000
Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards	180	6,583,000	180	7,283,000	180	7,283,000	204	8,545,000
Institutional awards	1412	51,344,000	1412	56,800,000	1412	56,800,000	1583	65,845,000
Total, Training	1592	57,927,000	1592	64,083,000	1592	64,083,000	1787	74,390,000
Research & development contracts	131	265,824,000	137	288,006,000	136	286,979,000	151	331,471,000
(SBIR/STTR)	(5)	(2,097,000)	(5)	(2,197,000)	(5)	(2,197,000)	(5)	(2,276,000)
	FTEs		FTEs		FTEs		FTEs	
Intramural research	1884	579,451,000	1991	653,226,000	1991	652,199,000	2015	722,274,000
Research management and support	771	141,483,000	815	160,433,000	815	160,433,000	825	179,503,000
Cancer prevention & control	324	461,572,000	344	514,151,000	344	514,151,000	348	570,473,000
Construction		3,000,000		5,000,000		5,000,000		5,000,000
Total, NCI	2979	3,740,127,000	3150	4,211,775,000	3150	4,209,721,000	3188	4,724,505,000
(Clinical Trials)		(648,622,000)		(701,000,000)		(701,000,000)		(785,300,000)

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Budget Authority by Activity 1/
(dollars in thousands)

ACTIVITY	FY 2001 Actual		FY 2002 Estimate		FY 2003 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:								
Cancer causation	908	$980,090	963	$1,100,170	970	$1,236,827	7	$136,657
Detection and diagnosis research	210	261,441	216	325,616	218	348,913	2	23,297
Treatment research	906	1,006,747	958	1,130,151	968	1,274,460	10	144,309
Cancer biology	490	588,610	518	656,985	527	732,526	9	75,541
Subtotal, Research	2514	2,836,888	2655	3,212,922	2683	3,592,726	28	379,804
Resource Development:								
Cancer centers support	21	282,061	22	307,790	28	359,190	6	51,400
Research manpower development	35	136,083	37	146,308	38	170,745	1	24,437
Construction	2	3,038	3	5,097	3	5,097	0	0
Subtotal, Resource Development	58	421,182	62	459,195	69	535,032	7	75,837
Cancer Prevention & Control	407	482,057	433	537,604	436	596,747	3	0
Total	2979	3,740,127	3150	4,209,721	3188	4,724,505	38	455,641

1/ Please see the following tables for the crosswalk from current law to proposed law to reflect the administration's proposal for full accrued retirement and health benefits.

National Institutes of Health

National Cancer Institute

2001 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2001 Actual Current Law	2001 Additional Accrual Costs	2001 Actual Proposed Law
Research:			
Cancer causation	$974,233	$5,857	$980,090
Detection and diagnosis research	260,086	1,355	261,441
Treatment research	1,000,902	5,845	1,006,747
Cancer biology	585,449	3,161	588,610
Subtotal, Research	2,820,670	16,218	2,836,888
Resource Development:			
Cancer centers support	281,926	135	282,061
Research manpower development	135,857	226	136,083
Construction	3,025	13	3,038
Subtotal, Resource Development	420,808	374	421,182
Cancer Prevention & Control	479,431	2,626	482,057
Total	3,720,909	19,218	3,740,127

National Institutes of Health

National Cancer Institute

2002 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2002 Appropriation Current Law	2002 Additional Accrual Costs	2002 Appropriation Proposed Law
Research:			
Cancer causation	$1,093,636	$6,534	$1,100,170
Detection and diagnosis research	324,151	1,465	325,616
Treatment research	1,123,652	6,499	1,130,151
Cancer biology	653,471	3,514	656,985
Subtotal, Research	3,194,910	18,012	3,212,922
Resource Development:			
Cancer centers support	307,641	149	307,790
Research manpower development	146,057	251	146,308
Construction	5,077	20	5,097
Subtotal, Resource Development	458,775	420	459,195
Cancer Prevention & Control	534,666	2,938	537,604
Total	4,188,351	21,370	4,209,721

National Institutes of Health

National Cancer Institute

2003 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2003 Estimate Current Law	2003 Additional Accrual Costs	2003 Estimate Proposed Law
Research:			
Cancer causation	$1,230,100	$6,727	$1,236,827
Detection and diagnosis research	347,401	1,512	348,913
Treatment research	1,267,746	6,714	1,274,460
Cancer biology	728,871	3,655	732,526
Subtotal, Research	3,574,118	18,608	3,592,726
Resource Development:			
Cancer centers support	358,996	194	359,190
Research manpower development	170,481	264	170,745
Construction	5,076	21	5,097
Subtotal, Resource Development	534,553	479	535,032
Cancer Prevention & Control	593,723	3,024	596,747
Total	4,702,394	22,111	4,724,505

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Summary of Changes

2002 Estimated budget authority				$4,209,721,000
2003 Estimated budget authority				4,724,505,000
Net change				514,784,000
	2002 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$223,264,000		$3,215,000
b. Annualization of January 2002 pay increase		223,264,000		2,565,000
c. January 2003 pay increase		223,264,000		4,169,000
d. Payment for centrally furnished services		111,434,000		10,029,000
e. Increased cost of laboratory supplies, materials, and other expenses		317,501,000		7,665,000
f. Accrued costs for retirement and health benefits		13,507,000		468,000
Subtotal				28,111,000
2. Research management and support:				
a. Within grade increase		73,108,000		1,239,000
b. Annualization of January 2002 pay increase		73,108,000		831,000
c. January 2003 pay increase		73,108,000		1,350,000
d. Payment for centrally furnished services		13,604,000		1,224,000
e. Increased cost of laboratory supplies, materials, and other expenses		73,721,000		1,780,000
f. Accrued costs for retirement and health benefits		5,529,000		193,000
Subtotal				6,617,000
3. Cancer prevention and control:				
a. Within grade increase		51,030,000		832,000
b. Annualization of January 2002 pay increase		51,030,000		593,000
c. January 2003 pay increase		51,030,000		963,000
d. Payment for centrally furnished services		4,187,000		377,000
e. Increased cost of laboratory supplies, materials, and other expenses		117,611,000		2,839,000
f. Accrued costs for retirement and health benefits		2,334,000		80,000
Subtotal				5,684,000
Subtotal, Built-in				40,412,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Summary of Changes--continued

CHANGES	2002 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,409	$1.386.479.000	32	$120,999,000
b. Competing	1,222	455.103.000	133	69,643,000
c. SBIR/STTR	315	86,361,000	42	15,000,000
Total	4,946	1.927.943.000	207	205,642,000
2. Centers	104	305,076,000	6	50,732,000
3. Other research	753	293.857.000	97	58,144,000
4. Research training	1,592	64,083,000	195	10,307,000
5. Research and development contracts	136	286,979,000	15	44,492,000
Subtotal, extramural		2.877.938.000		369,317,000
	FTEs		FTEs	
6. Intramural research	1,991	652.199.000	24	41.964.000
7. Research management and support	815	160,433,000	10	12,453,000
8. Cancer prevention and control	344	514.151.000	4	50.638.000
9. Construction		5,000,000		0
Subtotal, program		4.209.721.000		474.372.000
Total changes	3,150		38	514,784,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Budget Authority by Object

	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	3150	3188	38
Full-time equivalent of overtime and holiday hours	13	13	0
Average ES salary	$137,556	$141,820	$4,264
Average GM/GS grade	11.3	11.3	0.0
Average GM/GS salary	$66,071	$68,119	$2,048
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$70,821	$73,017	$2,196
Average salary of ungraded positions	$88,590	$91,337	$2,747

	OBJECT CLASSES	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$156,415,000	$168,325,000	$11,910,000
11.3	Other than Full-Time Permanent	67,314,000	72,300,000	4,986,000
11.5	Other Personnel Compensation	10,726,000	11,537,000	811,000
11.8	Special Personnel Services Payments	37,042,000	40,746,000	3,704,000
11.9	**Total Personnel Compensation**	**271,497,000**	**292,908,000**	**21,411,000**
12.0	Personnel Benefits	60,885,000	65,468,000	4,583,000
12.1	Personnel Benefits, Accrued Retirement Costs	15,020,000	15,529,000	509,000
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Cost, Current Law	**332,382,000**	**358,376,000**	**25,994,000**
	Subtotal, Pay Cost, Proposed Law	**347,402,000**	**373,905,000**	**26,503,000**
21.0	Travel and Transportation of Persons	12,778,000	14,182,000	1,404,000
22.0	Transportation of Things	1,242,000	1,379,000	137,000
23.1	Rental Payments to GSA	1,000	1,000	0
23.2	Rental Payments to Others	6,656,000	7,388,000	732,000
23.3	Communications, Utilities and Miscellaneous Charges	8,700,000	9,658,000	958,000
24.0	Printing and Reproduction	4,243,000	4,753,000	510,000
25.1	Consulting Services	17,092,000	19,684,000	2,592,000
25.2	Other Services	202,461,000	233,085,000	30,624,000
25.3	Purchase of Goods and Services from Government Accounts	350,396,000	379,598,000	29,202,000
25.3	Accrued Retirement Costs	6,350,000	6,582,000	232,000
25.4	Operation and Maintenance of Facilities	90,754,000	104,500,000	13,746,000
25.5	Research and Development Contracts	274,814,000	317,659,000	42,845,000
25.6	Medical Care	3,561,000	4,106,000	545,000
25.7	Operation and Maintenance of Equipment	14,659,000	16,899,000	2,240,000
25.8	Subsistence and Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services, Current Law**	**953,737,000**	**1,075,531,000**	**121,794,000**
25.0	**Subtotal, Other Contractual Services, Proposed Law**	**960,087,000**	**1,082,113,000**	**122,026,000**
26.0	Supplies and Materials	54,952,000	63,034,000	8,082,000
31.0	Equipment	31,840,000	36,721,000	4,881,000
32.0	Land and Structures	0	0	0
33.0	Investments and Loans	0	0	0
41.0	Grants, Subsidies and Contributions	2,781,723,000	3,131,268,000	349,545,000
42.0	Insurance Claims and Indemnities	4,000	4,000	0
43.0	Interest and Dividends	93,000	99,000	6,000
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs, Current Law	**3,855,969,000**	**4,344,018,000**	**488,049,000**
	Subtotal, Non-Pay Costs, Proposed Law	**3,862,319,000**	**4,350,600,000**	**488,281,000**
	Total Budget Authority by Object, Current	**4,188,351,000**	**4,702,394,000**	**514,043,000**
	Total Budget Authority by Object, Proposed	**4,209,721,000**	**4,724,505,000**	**514,784,000**
	Total Accrued Retirement Costs	**21,370,000**	**22,111,000**	**741,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Salaries and Expenses

OBJECT CLASSES	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$156,415,000	$168,325,000	$11,910,000
Other Than Full-Time Permanent (11.3)	67,314,000	72,300,000	4,986,000
Other Personnel Compensation (11.5)	10,726,000	11,537,000	811,000
Special Personnel Services Payments (11.8)	37,042,000	40,746,000	3,704,000
Total Personnel Compensation (11.9)	**271,497,000**	**292,908,000**	**21,411,000**
Civilian Personnel Benefits (12.1)	60,885,000	65,468,000	4,583,000
Accrued Costs of Retirement Benefits (12.1)	15,020,000	15,529,000	509,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs, Current Law	**332,382,000**	**358,376,000**	**25,994,000**
Subtotal, Pay Costs, Proposed Law	**347,402,000**	**373,905,000**	**26,503,000**
Travel (21.0)	12,778,000	14,182,000	1,404,000
Transportation of Things (22.0)	1,242,000	1,379,000	137,000
Rental Payments to Others (23.2)	6,656,000	7,388,000	732,000
Communications, Utilities and Miscellaneous Charges (23.3)	8,700,000	9,658,000	958,000
Printing and Reproduction (24.0)	4,243,000	4,753,000	510,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	17,011,000	19,592,000	2,581,000
Other Services (25.2)	202,461,000	233,085,000	30,624,000
Purchases from Govt. Accounts (25.3)	206,539,000	229,082,000	22,543,000
Accrued Retirement Costs (25.3)	6,350,000	6,582,000	232,000
Operation & Maintenance of Facilities (25.4)	19,162,000	22,028,000	2,866,000
Operation & Maintenance of Equipment (25.7)	14,659,000	16,899,000	2,240,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal, Other Contractual Services, Current Law	**459,832,000**	**520,686,000**	**60,854,000**
Subtotal, Other Contractual Services, Proposed Law	**466,182,000**	**527,268,000**	**61,086,000**
Supplies and Materials (26.0)	54,339,000	62,336,000	7,997,000
Subtotal, Non-Pay Costs, Current Law	**547,790,000**	**620,382,000**	**72,592,000**
Subtotal, Non-Pay Costs, Proposed Law	**554,140,000**	**626,964,000**	**72,824,000**
Total, Administrative Costs, Current Law	**880,172,000**	**978,758,000**	**98,586,000**
Total, Accrued Costs	**21,370,000**	**68,918,000**	**47,548,000**
Total, Administrative Costs, Proposed Law	**901,542,000**	**1,047,676,000**	**146,134,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2002 House Appropriations Committee Report Language (S. Rpt.107-229)

Item

Blood Cancers- The Committee is pleased that NCI has conducted a progress review group on lymphoma, leukemia and myeloma to evaluate opportunities for research in these areas and looks forward to receiving a copy of the final report. The Committee requests that the Director of the Institute be prepared to provide a progress report on lymphoma and hematological cancer research, including a proposed budget plan, at the fiscal year 2003 appropriations hearing. (p. 58)

Action taken or to be taken

The National Cancer Institute (NCI) had initiated a comprehensive review of the blood cancers program. The review process invited outside experts to review progress, the current state of science, and resource allocation to a variety of blood cancers. In May 2001, the Leukemia, Lymphoma and Myeloma (LLM) Progress Review Group (PRG) was convened. The report from this PRG is now available as a hard copy as well as on the NCI web site (http://cancer.gov). Since May, the Institute has carefully reviewed its LLM research portfolio to identify possible gaps and needs that are consistent with the recommendations of the Report. In November, 2001 the Institute convened a meeting of the PRG to discuss the reommendations in the report and to identify strategies to close these gaps. Closing these gaps will be the Insttitute's priority for LLM research. The NCI is now prepararing a plan for implementing the strategies identified at this meeting. The plan will be created by a working group of experts from across the Institute. This group will remain in place to oversee implementation and track progress. Once completed, the plan will be aggressively promoted to the scientific community and to patient advocates. NCI is prepared to discuss these research activities at the FY 2003 appropriations hearings.

The NCI and National Heart, Lung and Blood Institute (NHLBI) cosponsored an RFA (HL-01-004) entitled "Blood and Marrow Transplant Clinical Research Network". Fourteen clinical centers and one central operations office were cofunded by the two Institutes.

Benzene is an established human leukemogen and may also cause non-Hodgkin's lymphoma (NHL) and other cancers. However, its mechanism of action is uncertain and its ability to cause cancer at low levels of exposure is unknown. A study of healthy workers exposed to high levels of benzene in China was undertaken to identify mechanistically-based biomarkers that reflect the early biologic effects of benzene. An increased frequency of cytogenetic and genetic alterations in peripheral white blood cells was observed. These markers are relevant for leukemia, and support the hypothesis that benzene's mechanism of action is mediated through chromosomal

damage. An important remaining question is the biologic effect of low levels of exposure in the occupational setting and from environmental sources experienced by the general population. A new study will apply the biomarkers found to be most sensitive and specific for benzene exposure to determine if the cytogenetic and molecular events also occur among workers exposed to relatively low levels of benzene.

To address widespread concerns about cancer risks from residential magnetic field exposures, investigators from NCI and from the Children's Cancer Group have conducted a case-control study to evaluate the possible role of extremely low frequency magnetic field exposures (50- or 60-Hertz) from power lines and electrical appliances in risk of childhood leukemia. Neither high, directly measured residential magnetic field levels nor high wire code levels (a proxy measure for close distance of residence to power lines) were associated with significantly increased risks of childhood acute lymphoblastic leukemia. Exploratory analyses evaluating various alternative magnetic field exposure metrics including measures of central tendency (e.g., 30-70th percentiles), peak values, threshold levels, and rate-of-change metrics did not change the conclusions stated above, which were based on time-weighted average direct and proxy measures. Wire code categories were highly reproducible among wire coding technicians and were well-correlated with measured magnetic field levels. Based on interview data, risks were significantly elevated in offspring whose mothers reported use of an electric blanket during pregnancy. Acute lymphoblastic leukemia was also increased among children whose mothers reported postnatal use of electric blankets, hair dryers, video machines in arcades, and video games connected to televisions postnatally, but the patterns for duration or frequency of use of these appliances were inconsistent. While risks rose with increasing number of hours per day children spent watching television, risks were similar regardless of the usual distance from the television. In addition, data from a recent study revealed magnetic field exposures to be equivalent to background levels at distances that children typically sit while watching television.

HTLV-I infection is endemic in southern Japan, the Caribbean, parts of Africa, the Middle East, and South America. It is strongly linked to adult T-cell leukemia/lymphoma (ATL), a highly fatal non-Hodgkin's lymphoma, and to a neurodegenerative disease termed HTLV-I-associated myelopathy (HAM). Only about 5 percent of HTLV-I carriers, however, will develop ATL in their lifetime. Because most infected people remain well, efforts are focused on identifying clinical and biologic markers of disease progression. Acquiring infection early in life appears to be a risk factor for this malignancy. Most ATL cases and nearly all pediatric HTLV-I infections result from prolonged breast-feeding, especially after age 6 months, and some children develop infective dermatitis, which may be a harbinger of ATL. Significant differences between subjects with ATL, those with HAM, and those with asymptomatic HTLV-I infection were found in serum markers of immune activation and in human leukocyte antigen types. NCI’s large study of HTLV-I-infected families in Jamaica and Trinidad will use association and linkage analysis to clarify the relationships between host, environment, and disease manifestations of HTLV-I infection. To improve all HTLV-I/-II studies, a sensitive and specific assays have been developed to precisely quantify "proviral load” or the number of blood cells infected with HTLV-I/-II, “mRNA level”, the amount of virus replications in vivo, as well as cytokine levels.

The average age of ATL diagnosis in Japan is much higher than in the Caribbean. Risk of the disease is higher in males than in females among the Japanese, while the gender difference is not

apparent in the Caribbean. Understanding these differences in cancer risks across geographic areas remain one of the most important foci of NCI's HTLV-I research.

As patient survival following a diagnosis of cancer continues to improve, identification of the late consequences of therapy, including induction of a new malignancy, becomes critical. Quantification of the late effects of cancer therapy provides a singular opportunity for establishing dose-response relations since patients receive measured amounts of potentially cancer-inducing agents. Studies have shown that platinum-based chemotherapy for ovarian cancer was linked to a four-fold risk of leukemia; however, the substantial benefit that platinum-based treatment offers, outweighs the relatively small excess risk of leukemia. A study of leukemia following radiotherapy for testicular cancer revealed a three-fold elevated risk for leukemia, and this risk increased with increasing radiation dose to active bone marrow. Characterization of these risks enables clinicians to make informed decisions about treatment options, balancing efficacy against acute and chronic sequelae.

For the past 30 years, NCI has maintained a Familial Registry of families with two or more living cases of chronic lymphocytic leukemia (CLL). Based on the collection of medical records and biological specimens, NCI researchers have found that age of onset of CLL in the familial cases occurs approximately 10 years earlier than in sporadic cases. In addition, there is often a higher percentage of second primary tumors in these patients. A genome-wide search for susceptibility genes is in progress, as well as other laboratory investigations such as characterization of protein expression of candidate loci, cell surface marker analysis, characterization of telomerase activity in tumor cells, and analysis of expressed immunoglobulin heavy chains. Efforts to recruit new families in order to expand these studies are continuing through a newsletter posted at the CLL Family Registry News website: http://dceg.cancer.gov/hgp/geb/CLL/CLLnewsletter.html

NCI investigators will convene a meeting in 2002 to form a consortium of investigators with an interest in familial CLL to collaborate and share data. The proposed consortium will provide an opportunity for the members of an existing clinical consortium to collaborate with genetic epidemiologists to pursue linkage studies and candidate gene approaches. There are currently 234 clinical trials in leukemia of which 168 are NCI sponsored.

The increasing incidence of non-Hodgkin's lymphoma (NHL), which has nearly doubled over the past two decades, has prompted a number of epidemiologic studies to investigate this trend. NCI scientists are assessing the demographic patterns and trends in population-based rates of different histologic subgroups of NHL, which appear to be distinct entities with specific age, sex, racial, temporal, and geographic variations in rates. Findings from a large, population-based study reveal differing demographic patterns and incidence trends according to histologic group.

Epidemiologic research into the etiology of NHL has examined pesticide use, along with a wide range of other possible risk factors. In a multi-disciplinary case-control study of non-Hodgkin's lymphoma in the U.S., NCI scientists are measuring pesticide residues in household dusts, serum samples, and tap water, and collecting questionnaire data on the history of residential pesticide use. In addition, an ongoing study is investigating the risk of developing NHL from occupational exposures using a national data set from Sweden called the Cancer Environment

Register. NCI intramural researchers are also pursuing a past finding of increased risk of lymphatic and hematopoietic cancer among long-term users of dark hair coloring products in a collaborative study of NHL and multiple myeloma conducted with Yale University.

The Agricultural Health Study is a major effort designed to evaluate the relationship between pesticides and other agricultural factors and the risk of cancer and other diseases. Enrollment in this study includes about 90,000 men and women from Iowa and North Carolina. The study includes farmers, licensed private pesticide applicators, their spouses, and commercial pesticide applicators. The study participants will be followed to collect data on cancer incidence and mortality.

Organochlorines are ubiquitous environmental contaminants and suspected human carcinogens. To evaluate the influence of organochlorine exposure on risk of NHL, a nested case-control study was conducted within a cohort of nearly 26,000 healthy subjects in western Maryland. The study found that serum PCB levels were strongly associated with subsequent risk of developing NHL, and the effect was potentiated by seropositivity for the Epstein-Barr virus early antigen. These observations are being followed-up in similarly designed prospective studies.

Elevated nitrate levels in public drinking water supplies have also been associated with an increased risk of NHL in Nebraska. This hypothesis is being investigated further in ongoing case-control investigations of NHL in Iowa, Seattle, and the Detroit area.

The role of viruses, including HTLV-I, HHV-6, KSHV and EBV, in this disease is also being examined, and immune-related medical conditions and treatments, sunlight exposures, diet, hair dye use and other hypothesized risk factors are being assessed. Analytic approaches to synthesizing data collected from biospecimens, environmental samples, and computer-assisted questionnaires are also under development.

NCI scientists organized the first meeting of the International Consortium of Investigators Working on Non-Hodgkin's Lymphoma Epidemiologic Studies (Interlymph) in November 2001. The focus of the first meeting was to develop strategies such as using common histopathological, immunophenotypic, cytogenetic, and molecular classifications among the different epidemiologic studies and developing methodological approaches to evaluate the potential role of viruses and other etiologic factors in case-control studies. The meeting also explored the role of specific genetic polymorphisms and genetic pathways that may be etiologically important in NHL and considered ways to collectively undertake a large study of multiplex families (those with one or more cases of NHL and related lymphoproliferative malignancies, along with other possibly related cancers in close relatives). Future meetings will continue to develop these ideas, prepare protocols for collaborative efforts on these topics, and address other aspects of the studies, including occupational data, exposure to solar radiation derived from interviews, dietary factors, and other genetic features. There are currently 185 clinical trials in Non-Hodgkin's lymphoma of which 123 are NCI sponsored.

A population-based case-control study in three geographic areas of the U.S. examined differences in incidence between blacks and whites for a variety of cancers, including multiple myeloma. Elevated risks were found to be associated with obesity, while reduced risks were

related to eating cruciferous vegetables and fish and taking vitamin supplements, particularly vitamin C. The greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may explain part of the higher incidence of multiple myeloma among blacks compared to whites in the United States. Findings from another study highlighted low occupation-based socioeconomic status (SES), low education, and low annual family income as risk factors that could account for a substantial amount of the black/white differential in the incidence of multiple myeloma. NCI investigators are continuing their efforts to explore other risk factors associated with the race-related difference in incidence rates for multiple myeloma.

Myelodysplastic syndrome (MDS) is characterized by peripheral blood cytopenias in the presence of a cellular or hypercellular marrow. Satisfactory therapy, in the form of hematopoietic stem cell transplantation, is available only to a small proportion of patients. New treatment modalities are needed. NCI funded a grant from the Fred Hutchinson Cancer Research Center last fiscal year using novel therapeutic strategies in this disease. The rationale of the clinical trials is based on data that MDS is a disease of enhanced apoptosis activation via the Fas-Fas ligand system through blockage of Fas-Fas ligand binding to bone marrow cells. Thus the efficacy of TNFR:Fc (a soluble TNF receptor), antithymocyte globulin (an anti-T cell agent), and flt-3 ligand (an early activating cytokine) alone and in combination will be tested to determine whether peripheral cytopenias is improved and hematopoiesis is stabilized in the marrow of these patients.

On February 1-2, 2000, October 30-31, 2000, and June 11-12, 2001 respectively, the Cancer Therapy Evaluation Program (CTEP) held State of Science Meetings on Myelodysplastic Syndromes, Acute Myeloid Leukemia and Chronic Lymphocytic Leukemia. The State of Science Reports for the first two Meetings are currently available on the CTEP web site (http://ctep.cancer.gov). The latter Report on CLL is in the process of being published and should be available soon on the same web site.

The most striking advances in leukemia treatment research have been made in two diseases, Acute Promyelocytic Leukemia (APL) and Chronic Myelogenous Leukemia (CML). These new therapies all involved a molecularly targeted approach to treatment. All-trans retinoic acid and arsenic trioxide have increased the cure rate of actue promyelocytic leukemia. All trans retinoic acid was approved several years ago by the FDA and targets the retinoic receptor. Trisenox (arsenic trioxide) from Cell therapeutics received approval from the FDA on September 25, 2000 for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression. Gleevec (STI571) from Novartis Pharmaceuticals Corporation received approval on May 10, 2001 for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is a specific inhibitor of the Bcr-Abl specific tyrosine kinase.

Mylotarg (gemtuzumab ozogamicin), a monoclonal antibody for injection, from Wyeth-Ayerst Research received approval on May 17, 2000, for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. Compounds that inhibit angiogenesis are of particular interest to NCI for blood cancers. The drugs being studied include thalidomide and an

anti-VEGF monoclonal antibody, bevacizumab. There are currently 108 clinical trials in Non-Hodgkin's lymphoma of which 79 are NCI sponsored.

Item

Blood Cancers **--** The Committee urges NCI to enhance research support to improve the understanding of, and develop treatments for, myelodysplasia, a serious blood disorder affecting primarily older Americans and individuals who have previously undergone radiation or chemotherapy treatment for cancer. (p. 58)

Action taken or to be taken

Please refer to pages NCI-39 through NCI-44 of this document for NCI's response to this significant item regarding Blood Cancers.

Item

Bone Disease- The Committee encourages NCI to include multiple myeloma, a cancer of the plasma cells of the bone marrow, in its study of bone involvement in certain cancers. The Committee urges NCI to collaborate with NIAMS in translational research activities to capitalize on recent advances in the study of biophosphonates, a class of drugs that strengthen bone through all available mechanisms, as appropriate. (p. 58)

Action taken or to be taken

Multiple myeloma and childhood skeletal malignancies (Osteosarcoma and Ewing's sarcoma) are cancers of bone origin. Both (bone) cancer metastases and multiple myeloma are separate Significant Items and we also refer you to those responses for additional information.
Osteosarcoma and Ewing's sarcoma account for the majority of childhood bone tumors, 56% and 34% respectively. Through a series of national pediatric clinical trials conducted by the pediatric oncology cooperative groups (now the Children's Oncology Group, COG) over the past three decades, the 5-year survival rate has improved such that more than 70% of children with newly diagnosed non-metastatic osteosarcoma or Ewing's sarcoma can expect to survive long term. Furthermore, advances in pediatric orthopedic surgery, chemotherapy and radiotherapy have allowed the majority of children with localized disease to undergo limb-sparing procedures, thus diminishing the long-term impact of their childhood cancers. Approximately 20-30% of children, however, are diagnosed with metastatic bone disease and their survival is 50% or less. While children with these tumors have benefitted from the historically high-level of participation in pediatric oncology clinical trials, the level of participation and gains in survival outcome by adolescents and young adults of these malignancies has been less dramatic. COG and NCI have begun an Adolescent-Young Adult Initiative to increase clinical trial participation by this group of patients. This initiative will involve the cooperation of the adult cooperative groups.
The COG Bone Tumor Committee conducted a special symposium on bone sarcoma biology in November 2000. A meeting entitled "Biology of Childhood Osteogenic Sarcoma and Potential Targets for Therapeutic Development" will take place in Bethesda in November 2001. This meeting will be cosponsored by the NCI, the NIH Office of Rare Diseases and the COG.

Current research efforts among COG investigators are focused on the molecular biologic characteristics of a patient's tumor at diagnosis that can be used prospectively to predict the tumor's metastatic potential, therapy responsiveness and the patient's survival prognosis. Their ultimate goal is to develop a set of biologic prognostic indicators that can be used to stratify patients by risk of relapse as well as to provide a basis for adjustment in the intensity of treatment. A variety of genes, including drug resistance genes, tumor suppressor genes, oncogenes and genes related to the tumor cell environment are being investigated. COG investigators have received funding from the "NCI Director's Challenge: Towards a Molecular Classification of Cancer" to use microarray technology to study gene expression profiles of pediatric sarcomas.

Other research activities are centered on exploring new approaches to the treatment of osteosarcoma and Ewing's sarcoma. Forty to sixty percent of osteosarcomas have an amplification or overexpression of the mdm2 gene. The mdm2 oncoprotein binds to the p53 tumor suppressor protein and serves as a negative regulator of p53. Investigators at the University of Alabama have hypothesized that mdm2 may play a role in determining the efficacy of certain chemotherapeutic agents that act on the p53-mediated apoptosis pathway. They believe that by inhibiting mdm2 expression, the amount of mdm2 oncoprotein will be reduced which will diminish the mdm2 negative feed-back inhibition of p53, thus resulting in a significant increase of functional p53 levels that will modulate p53-mediated therapeutic effects. Using an osteosarcoma mouse model, investigators at MD Anderson Cancer Center are delivering an aerosolized formulation of liposomal 9-nitro-camptothecin, an active chemotherapy agent, directly into the lung to treat metastatic disease. Additionally, an inhaled adenoviral vector containing IL-12 is being studied in these mice to determine whether the induction of IL-12 production in the lungs decreases the growth and development of metastatic lung nodules. They plan to translate this approach into a Phase I clinical trial using a combination of aerosolized liposomal camptothecin in combination with inhaled adenoviral vector containing IL-12 for children with osteosarcoma metastatic to the lungs.

The COG recently completed a randomized prospective trial that examined the impact of adding ifosfamide and muramyl tripeptide to standard cisplatin, doxorubicin and high dose methtrexate therapy on event free survival of osteosarcoma patients. A nationwide series of pilot studies are underway to evaluate the use of more intensive alkylator therapy and the adjustment of chemotherapy intensity based on the degree of histologic necrosis during induction therapy. Furthermore, COG has initiated a Phase II trial of Trastuzumab (Herceptin) in metastatic osteosarcoma patients with tumors that overexpresses HER2 and has completed a Phase II trial of Topotecan in patients with metastatic osteosarcoma.

The COG recently completed a randomized prospective trial among children with Ewing's sarcoma that compared conventional chemotherapy versus a regimen of shorter duration including more intensive alkylating agent dosing. A new Phase III trial comparing conventional chemotherapy to a regimen using chemotherapy interval compression to increase dose intensity is now underway. The COG also recently completed a trial investigating the role of high dose chemotherapy and radiation followed by autologous stem cell reconstitution as consolidation for newly diagnosed patients with high-risk metastatic disease.

There are numerous Phase I studies currently open that are for children with relapsed osteosarcoma and Ewing's sarcoma. The agents include cytotoxic agents including Rebeccamycin, continuous infusion Topotecan, Ironotecan, Irinotecan/Vincristine, and an Irinotecan/Cisplatin combination therapy. Current and planned trials of molecularly targeted agents include Fenretinide, Flavopiridol, ZD1839, ET-743, PS-341, Squalamine/Carboplatin, and STI-571. Immunotherapy in the treatment of children with Ewing's sarcoma is being studied using an immunomodulatory agent (a macrophage activating agent, liposome-encapsulated muramyl dipeptide (ImmTher). This dipeptide stimulates the pulmonary immune system to destroy tumor cells.

Bisphosphonates, analogs of endogenous pyrophosphates in our bodies, are potent inhibitors of bone resorption. This class of compounds is used to treat/palliate primary bone cancers as well as metastatic cancers to the bone. Newer more potent derivatives of bisphosphonates, the aminobisphosphates (ibandronate and zoledronic acid) are currently in clinical trials. Zometa (zoledronic acid) from Novartis Pharmaceuticals Corporation, received approval on August 20, 2001, for the treatment of hypercalcemia of malignancy. A number of other types of anti-bone resorptive agents are entering early clinical trials including integrin inhibitors, osteoprotegerin, and anti-parathryoid-related peptide antibodies.

Item

Cancer Metastases- The Committee encourages NCI to conduct research to develop a better understanding of the unique role bone microenvironment plays in cancer metastatic to bone, in particular, in breast cancer, prostate cancer and myeloma through all available mechanisms, as appropriate, including the development of animal models of bone metastases and the identification of novel therapeutic targets and modalities to prevent and treat bone metastases. (p. 58)

Action taken or to be taken

Breast and prostate cancer metastasizes frequently to the skeleton and cause considerable morbidity and deterioration of the quality of life. The clinical consequences of bone metastasis are bone pain, bone fractures, increased calcium in the blood and nerve compression. Currently, only palliative treatment is available. A better understanding of the processes involved in the "homing" of cancer cells to bone, tumor growth in the bone, and subsequent destruction of the normal bone architecture is needed before optimal methods for the prevention and treatment of bone disease can be developed. As the basic mechanisms that drive this intricate process are elucidated, potential points of intervention can be identified as targets for therapy.

The NCI is using a multi-pronged approach to increase our understanding of the unique role the bone microenvironment plays in metastasis of cancer to the bone. The NCI has actively encouraged the exchange of information, resources, and model systems between members of the developmental bone biology and basic cancer biology research communities. A special Program Announcement "Molecular and Cellular Biology of Metastatic Tumor Cells" encourages investigators to submit novel applications in the area of tumor metastasis. This initiative has been supported for the last several years. In addition, two workshops were organized in

September and November 2000 by NCI staff. The first entitled: “Epithelial Stromal Interactions and Tumor Progression: Meeting Summary and Future Directions,” was geared to getting a state-of-the-art assessment of our current knowledge of tumor interactions with its neighboring cells. Presentations made by cancer cell biologists and clinical oncologists provided a firm realization of reciprocal interactions between tumor cells and its stroma. It was clear that tumor cells cannot survive without interacting with its neighboring cells during all phases of tumorigenesis - beginning with early tumor growth and later on during angiogenesis and metastasis.

The second workshop entitled "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities," was focused exclusively on bone microenvironment and metastasis. The workshop covered three major cancers metastatic breast and prostate cancer, and myeloma. The workshop, which brought together scientists and clinicians working in various areas related to bone biology, provided a comprehensive picture of the complex extracellular matrix of the bone and identified potential mediators of cancer cell metastasis. The discussions in the workshop covered these major areas: i) an understanding of the unique features of the bone and its microenvironment that render it an attractive site for tumor cells; ii) ideal experimental models that were useful in studying bone metastasis; and iii) possible targets in the bone that could be used in directing therapy once metastasis has occurred.

A major contribution to our understanding of the process of bone metastasis has been the demonstration that the bone microenvironment critically influences the behavior of cancer cells that metastasize to bone. The bone microenvironment alters the phenotype (tumor aggressiveness) of metastatic tumor cells in a manner that changes tumor behavior. Furthermore, some of the molecular mechanisms responsible for the bidirectional interaction between bone and tumor cells in vivo have been recently identified.

Studies have shown that human breast cancer cells, both from the primary tumor and visceral metastasis, express low levels of a protein PTHrP. However, 90% of breast cancer cells that spread to the bone express this protein. PTHrP levels are enhanced in human breast cancer cells when they interact with the bone microenvironment, and blocking PTHrP expression has been shown to decrease bone metastasis. At least one culprit involved in increased PTHrP production is a growth factor, TGF- ß and blocking the action of this growth factor decreases the production of PTHrP. Since bone metastasis have high morbidity and mortality, this is an important area of research that will be further explored.

Another example of the specific interaction between human cancer cells and bone cells is also seen in patients with breast cancer. Endothelin-1 (ET-1) is a protein produced by human breast cancer but it has many functions in the bone. While ET-1 promotes bone formation, it retards bone resorption. ET-1 has been shown to promote tumor progression of breast cancer. Blocking ET-1 can selectively inhibit tumor cell growth in the bone with no effect on tumor cell growth in other organs. Future effort is being targeted in developing specific inhibitors which either halt or reduce the growth of bone metastasis.

Bone destruction is also a major source of morbidity and potential mortality in patients with multiple myeloma. It is now known that when myeloma cells bind bone marrow stromal cells there is an enhanced production of a protein called IL-6 by marrow stromal cells. IL-6 has a

two-pronged negative effect on myeloma cells - it not only causes proliferation of myeloma cells but also reduces the rate of their cell death - resulting in a rapid accumulation of myeloma cells in the bone.

Another protein RANK ligand (RANKL), is also produced when myeloma cells interact with the bone stromal cells. RANKL stimulates osteoclast formation - cells that destroy bone, thus resulting in bone destruction. Using experimental models of breast cancer and myeloma, investigators have shown that factors which block osteoclastic bone destruction, such as bisphosphonates, can have not only retard bone destruction but inhibits tumor growth in the bone as well.

A unique protein produced by 70% of myeloma cells is MIP-1 alpha, which has profound deleterious effects - increased bone destruction, and increases tumor burden. Using experimental models of myeloma, it has been shown that blocking MIP-1 alpha activity selectively decreases tumor cell homing to bone marrow but not to soft tissues. This is another example of the unique interactions that exist between tumor cells and different microenvironments.

Interactions between tumor cell and bone stromal cells can also make tumor cells more resistant to chemotherapy. Work from several laboratories suggests that adhesive interactions between myeloma cells and stromal cells in the bone microenvironment lead to enhanced production of cytokines that cause osteoclastic bone resorption and can result in resistance to chemotherapy. Such results provide a hope that interference with the process of bone destruction (e.g., with bisphosphonates) or inhibiting the strong interactions between tumor cells and bone stromal cells (using "anti adhesive" agents) can not only reduce the bone loss but also reduce or prevent tumor burden in the bone. Indeed, recent studies using animal models as well as in patients, have shown that bisphosphonates which reduce bone loss can also reduce tumor burden. This observation has led to many important additional questions that need to be systematically addressed.

Many of the molecular mechanisms responsible for bone metastasis are just beginning to be delineated using experimentally induced animal models of breast and prostate cancer metastasis. The role of several different types of proteins like growth factors, proteases and adhesive proteins has recently been recognized. For example, the importance of a specific protein (urokinase) in skeletal metastasis of prostate cancer cells has been reported. These data suggest that these factors are potential molecular targets for the development of therapies aimed at reducing bone destruction and bone metastasis and that targeting multiple steps involved in the metastatic process may be more effective than inhibiting one.

NCI supports the development of reliable and predictive animal models that will determine the specific molecular mechanisms involved in the step-wise process of bone metastasis in vivo. An in vivo approach is the most rational avenue to develop new and specific therapies for preventing or treating osteolysis associated with malignancies, and then testing their efficacy in preclinical studies. These different models should enable mechanisms to be elucidated and contribute background information for the design of further clinical trials. Some of these models are briefly highlighted below:

- Establishment of spontaneous human tumors in nude mice that replicate the clinical syndrome of hypercalcemia in patients and will aid in evaluating novel approaches to diminish PTHrP production;
- Development of several models of myeloma bone disease which closely mimics human myeloma bone disease;
- Direct injection of breast tumor cells into the heart has resulted in tumor colonization of bone. Recently a new model of spontaneous mammary carcinoma metastasis has been developed which uses the 4T1 mouse cancer cells. These cells, when inoculated into the mammary fat pad, cause metastasis in the liver and lung and bone, mimicking the complete process of human breast cancer cell metastasis to bone from the primary breast site;
- The intracardiac injection of tumor cells (explained above) also results in metastasis which add new bone in the host (osteoblastic metastasis) - in both breast and prostate cancer. This is the first such model of osteoblastic metastasis. Breast cancer is a reasonable model of osteoblastic metastasis since osteoblastic metastasis occurs in 20% of patients with metastatic breast cancer, and is thus clinically important. It will be important to compare models of osteoblastic metastasis in the case of either prostate or breast cancer metastasis to the bone.

Recently, scientists supported by the NCI have developed novel mouse models in which human adult bone is transplanted in mice. Injection of human prostate tumor cells (intravenous or intra-cardiac) results in preferential metastasis to the human bone only and not the mouse bones. This models closely replicates the human disease. Analysis of the bone-tumor interaction after injection of tumor cells revealed the strong presence of PTHrP, TNF alpha and IL-6, these three proteins that have been associated with bone destructive activity in human prostate cancer. These results also provided the evidence that tumor cells induce a bone destructive response that enhances their ability to colonize the bone. This animal model allows us to study the biologic interaction between human prostate cancer cells and human bone and may enhance our understanding of the events associated with prostate cancer metastasis to bone.

The Mouse Models of Human Cancers Consortium (MMHCC), launched in September 1999, assembles multidisciplinary teams of scientists who are dedicated to the collaborative development, characterization, and validation of mouse models that are analogous to human cancers. 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 specific focus: such as genetic technology, prevention models, or site-specific models. In response to opportunities raised in the recent workshop on "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities", members of the MMHCC will convene a task force to explore the best strategies in mouse-modeling and small animal imaging strategies that capitalize on what is currently known regarding human cancer bone metastasis. This task force will include experts from basic, translational, and clinical research, and will evaluate the most promising and effective approach to generate new mouse models of breast, prostate and other cancers that metastasize to bone.

The NCI also supports new initiatives in drug development, based on the progress made over the last decade in our understanding of the biology of cancer cells. New technology, such as

combinatorial chemistry and the miniaturization of assays, will allow for the evaluation of thousands of compounds in a very short time and thereby speed up the process of identifying new candidates in clinical trials. Research areas of particular interest include pathways directing apoptosis (programmed cell death), invasion and metastasis, and the multiple molecular components that drive the cell cycle or are responsible for the repair of damaged DNA.
The NCI is co-sponsoring two workshops in 2002 which will address the issue of bone metastasis. The first is the "Third North American Symposium on Skeletal Complications of Malignancy" jointly sponsored by The Paget Foundation, Penn State College of Medicine, and the NCI, which will be held in April 2002. This workshop will bring together scientists and clinical investigators from relevant disciplines and will focus on the basic biology of tumor microenvironment, and basic and clinical aspects of bone metastasis with a focus on breast and prostate cancer, and multiple myeloma. The second workshop will be held in Prouts Neck, Maine in November 2002 and will focus exclusively on prostate cancer. In addition, NCI will continue to support special small workshops that deal with various aspects of angiogenesis and metastasis.

Since angiogenesis or the development of new blood vessels that feed a tumor, is a crucial step in bone metastasis, NCI is conducting and supporting extensive research into the causes of angiogenesis, as well as ways to reverse the process. Through its research programs, NCI is continues to expand its understanding of both metastasis and angiogenesis.

Breast and prostate cancer were two of the first cancers in which the role of angiogenesis in the spread of the tumor and survival of the patient was identified. In prostate cancer, increase in tumor angiogenesis has been shown to correlate with tumor spread. Many of the tumor-produced substances that promote tumor angiogenesis, such as the vascular stimulatory molecule vascular endothelial growth factor (VEGF), TGF alpha, and bFGF, are also associated with prostate cancer proliferation, progression, and dissemination. Researchers have also identified a new class of chemokines that play a pivotal role in tumor progression and angiogenesis. In breast cancer, researchers have found that in immunodeficient mice, human breast cancer cells produce a substance called MCP-1. When the mice were treated with antibodies to MCP-1, survival was extended and growth of micrometastasis was greatly diminished. Any agent that can inhibit the expression or activity of these tumor-derived substances that promote angiogenesis, or inhibit the proliferation and spread of cancer cells, are strong candidates for potential inhibitors of prostate and breast cancer metastasis.

NCI intramural scientists have been extending their studies examining the role of chemokines in angiogenesis in metastatic breast cancer. The chemokine, IL8, has been shown to promote growth of small cell lung carcinomas in vivo due to pro-angiogenic effects. Various human breast carcinoma cell lines were found to produce IL8 and other pro-angiogenic chemokines. Interestingly, treatment of immunodeficient mice bearing a human breast carcinoma cell lines with a human IL8 monoclonal antibody produced no protective effects. However, marked and synergistic anti-tumor effects were achieved when this antibody was combined with an anti-EGF receptor antibody that is currently being evaluated clinically. These results indicate that combination approaches using chemokine blockade and other forms of immunotherapy may result in greater anti-tumor effects in metastatic breast cancer.

Thus, there is tremendous opportunity for advancing research on understanding the bone microenvironment and bone metastasis. There are important new models currently available, as well as, additional ones under development. New findings on the role of the bone microenvironment in altering the behavior of tumor cells should lead to the development of innovative therapeutic agents to treat these diseases. Some of the specific questions that need to be addressed in the near future are:

- What are the adhesive interactions that exist between tumor cells and their microenvironment that are important in metastasis, tumor cell homing, and tumor growth? Identification of these interactions is an important areas to pursue.
- What are the tumor cell products that are responsible for enhancing tumor cell - bone microenvironmental interactions resulting in enhanced tumor growth and organ dysfunction?
- What can be done to alter the microenvironment so that it less hospitable to tumor growth and tumor cell homing?

NCI currently supports research in the use of quantitative computerized tomography, in conjunction with structural rigidity analysis, for monitoring fracture risk associated with skeletal metastasis in breast and prostate cancer patients. The objective of this study is to determine if the structural rigidity of bone altered by skeletal metastasis provides a better guideline for predicting pathological fracture than current clinical and radiographic criteria.

Preliminary data indicate that fracture rates for the subjects are lower than anticipated following the use of bisphosphonates as well as the curtailment of strenuous activities by the patients (i.e. Lifting heavy objects). Furthermore, many of the vertebrae calculated to be at risk for fracture do not necessarily contain the largest defects, but have smaller defects contained in very osteopenic surrounding bone that might reflect coexistent osteoporosis. This latter observation emphasizes the importance of calculating fracture risk based on the structural properties of the entire vertebra, rather than based on the size of the lesion alone.

Item

Chronic Lymphocytic Leukemia - Chronic Lymphocytic Leukemia (CLL), the most common form of adult leukemia in the United States, is characterized by an accumulation of abnormal lymphocytes in the blood and bone marrow. The Committee understands that NCI awarded a program project grant last year to establish and lead a multi-disciplinary national research consortium to study CLL at both the cellular and clinical levels. The Committee encourages NCI to consider expanding the scope of research activities of the consortium through all available mechanisms, as appropriate. (p. 59)

Action taken or to be taken

For the past 30 years, families with two or more living cases of chronic lymphocytic leukemia (CLL) have been enrolled within the NCI Familial Registry. Medical records and biological specimens have been collected for these subjects. Based on the collection of these data, NCI researchers have found that age of onset in familial cases is approximately 10 years earlier than in sporadic cases, and that there is often a higher percentage of second primary tumors in these

patients. These families provide an ideal opportunity to conduct whole genome searches, to study candidate genes, and to evaluate other biomarkers in investigating the etiology of this disease. Efforts to recruit new families in order to expand the search for a susceptibility gene are continuing through a newsletter posted at the CLL Family Registry News website: http://dceg.cancer.gov/hgp/geb/CLL/CLLnewsletter.html

A genome scan has been conducted in a sample of multiplex families with a history of CLL to detect underlying susceptibility genes. Linkage analyses are in progress, and areas of the genome showing positive results, as well as regions containing candidate genes, will be followed up with denser markers. Of particular interest is a region of 13q14, which is frequently deleted in CLL tumor cells, and some candidate genes in this region are being sequenced. Another preliminary linkage study has been conducted in 18 multiplex families to investigate the candidate gene, *ATM*. Other collaborations are underway to conduct cytogenetic tests on stored material from the familial cases. A putative precursor condition for CLL in these families, B-cell monoclonal lymphocytosis (BCML), is also under investigation. Additonal laboratory investigations include characterization of protein expression of candidate loci, cell surface marker analysis, characterization of telomerase activity in tumor cells, and analysis of expressed immunoglobulin heavy chains.

Ongoing studies are attempting to better elucidate the clinical heterogeneity observed in this disease in order to identify patients who will have an aggressive course. Biomarkers, such as CD38 expression and telomere length, are under study to evaluate their utility as markers of disease progression. In order to expand these studies, NCI investigators will convene a meeting in 2002 to form a consortium of investigators with an interest in familial CLL to collaborate and share data. The proposed consortium will enrich ongoing scientific investigations by providing the members of an existing clinical consortium the opportunity to collaborate with genetic epidemiologists to pursue linkage studies and candidate gene approaches.

CLL is the most frequent form of leukemia in adults in the United States. The current age-adjusted incidence rate is estimated to be 2.3/100,000. Chlorambucil, an alkylating agent, has been the standard treatment for CLL for 40 years but has not changed the natural history of the disease. Fludarabine, a nucleoside analogue, has been found to be effective in patients who had no response to chlorambucil, and has shown promise in several uncontrolled trials as initial therapy. There are currently no standard options for patients who relapse after responding to fludarabine. No drug combination has been demonstrated to be better than single agents in a randomized trial.

The CLL Research Consortium (CRC) funded by a P01 grant has made significant progress on the genetics, biochemistry, immunology, pharmacology and clinical studies on this disease. Microarray analyses on the genes expressed in CLL samples obtained from patients undergoing therapy have revealed that these samples could be segregated into two groups, each with a distinct gene expression pattern. The leukemia cells of group I were found to express non-mutated immunoglobulin genes, whereas the leukemia cells of group II expressed immunoglobulin genes that had undergone somatic mutation. Otherwise, these leukemia cells were indistinguishable from each other by morphology and surface antigen phenotype. Patients in group I were found to have a significantly more aggressive clinical course, generally

requiring therapy within 2-3 years from initial diagnosis. However, patients in group II had a more indolent course and did not require therapy until several years after the diagnosis. This observation has led to the hypothesis that CLL is actually two diseases with different genetic, biochemical, immunologic properties and that may respond differently to pharmacological or biologic therapies. Ongoing clinical studies have yielded promising treatment approaches. These include gene therapy approaches with Ad-CD154 vectors, and novel combination chemotherapy approaches with fludarabine and nelarabine. Four patients treated with the AD-CD154 vectors, experienced a beneficial clinical response as assessed by a prominent decrease in circulating malignant lymphocytes after treatment. Seven of 13 patients (55%) treated with the fludarabine plus nelarabine combination had objective responses. New compounds ready to be tested in the CRC clinics include Clofarabine, depsipeptide, PS-341, BMS-214662 and KRN5500. The capabilities and activities of the CRC have been expanded last fiscal year through a supplement provided to the P01. The funds will be used for improved data management capabilities, closer clinical monitoring, and increased tissue acquisition and molecular analysis. An interactive public web site (http://cll.ucsd.edu) has been established and is pending refinement.

NCI also supports CLL research activities under the Quick Trials mechanism (R21), R01 grants, and U01 and U10 cooperative agreements. Phase I clinical trials using humanized B10 monoclonal antibodies, R115777, LMB-2 and a combination of bryostatin and fludarabine are ongoing. Current Phase II trial agents include flavopiridol, arsenic trioxide, Campath-1H, dolastatin and gemcitabine. Phase II clinical trials using combinations of agents are being performed. Data from a CALGB study using fludarabine plus rituximab suggests that this combination is more effective than either drug used alone. A Phase III trial with this combination is being planned. A randomized Phase III clinical trial comparing fludarabine versus its combination with cyclophosphamide is being performed by the Eastern Cooperative Oncology Group. On May 7, 2001, Campath-1H was approved by the FDA for the treatment of patients with B-cell CLL who have been treated with alkylating agents and who have failed fludarabine therapy.

On June 11-12, 2001, the NCI convened a meeting to address the state of current clinical research pertaining to CLL. The summary of the meeting will be available on http://ctep.cancer.gov the broad goals and general objectives of this NCI State of Science meeting were as follows: (1) identify CLL studies and trial protocols to commence within the next 18-24 months; (2) identify CLL studies to commence within the next 2-5 years; (3) determine appropriate correlative studies to be undertaken; and (4) identify the resources that will be needed for future studies and clinical trials.

A major advance in the treatment of CML was reported last fiscal year. On May 10, 2001, the FDA approved Gleevec for the treatment of patients with CML in blast crisis, in accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec or STI571 is a small molecule that acts as an enzyme inhibitor of the BCR-ABL associated tyrosine kinase. STI 571 is very effective in patients with the chronic phase of the disease, is efficacious even in previously treated patients who are resistant to other forms of chemotherapy and also has reasonable activity during the blast crisis phase of the disease.

Item

Five a Day Nutrition Program- The Committee commends the NCI's national 5-A-Day program and encourages the Institute to conduct research on how best to promote healthy eating, especially fruit and vegetable consumption. This research should include, but not be limited to, research on children and adolescents, the general adult population, low-income and disparate groups, especially African Americans and Latinos and ways to transfer already-developed technologies to other government agencies and to non-profit, civic, and other organizations. (p. 59)

Action taken or to be taken

The NCI supports behavior change and communications research to determine effective strategies for increasing vegetable and fruit consumption. Behavioral change research in community interventions to increase vegetable and fruit consumption has shown positive results. Strategies to help Americans increase vegetable and fruit consumption have achieved a significant increase in intake among populations, specifically worksites, schools, churches, and supplemental food programs. NCI has conducted extensive consumer research to better understand motivators and barriers to eating more vegetables and fruit. The Institute also is expanding media outreach in an effort to increase the public's knowledge and awareness of the message that eating at least 5 servings of vegetables and fruit a day can reduce the risk of cancer and other chronic diseases.

Conducting research on how to best promote healthy eating, especially fruit and vegetable consumption, among children and adolescents, the general adult population, and low-income and disparate groups is a priority of NCI and the 5 A Day for Better Health Program.

- NCI and the American Cancer Society are collaborating to disseminate and evaluate a church-based nutrition education program for African Americans, a group at increased risk for most cancers. The program is based on two NCI-funded research studies that were highly successful in increasing fruit and vegetable consumption in African American populations.
- NCI has published a series of papers on fruit and vegetable intake by children and adults in the U.S., and reported the data by various subgroups of the population characterized by age, sex, race, ethnicity, income, education, and region. These data have been instrumental in providing greater specificity to national health objectives related to fruits and vegetables.
- NCI is conducting an analysis of school-based nutrition interventions that focus on increasing consumption of fruits and vegetables among children in grades K-12. After extensive review and testing of findings, a school-based nutrition kit comprised of evidence-based best practices is being developed for dissemination to schools and communities. A second project to review and evaluate worksite-based nutrition intervention for dissemination to communities is underway.

Conducting communications research and using program channels such as the mass media, restaurants, supermarkets, schools, and faith organizations are major initiatives of the 5 A Day for Better Health Program.

- NCI conducted extensive research among African American and Latino groups in the last year. Building upon previous work, the purpose of this current research was to identify topics and concepts for refreshing the 5 A Day program message. Results are now being applied to the planning and development of a new 5 A Day ethnic minority outreach initiative. Technologies such as CD-ROM and Internet, television, radio and the use of focused, tailored messages specific to the needs of the individual are currently being explored as a means to reach minority and ethnic audiences with the 5 A Day message and positively effect behavior change.
- The 5 A Day program is unique in that it relies heavily on private industry to achieve its goal of increasing vegetable and fruit consumption. Several national grocery store chains such as Safeway, Kroger, Albertson's, and Supervalu participate in the program, as do many produce growers, distributors and trade organizations. Recently, several nonprofit organizations and federal agencies became formal partners, including the American Cancer Society, the Centers for Disease Control and Prevention and the National Alliance for Nutrition and Activity.
- Now in the fourth year, NCI's popular news inserts featuring Chef Graham Kerr promoting science-based 5 A Day messages and practical tips for healthy eating is airing on over 70 television stations and being promoted to over 1,700 radio stations, including nationally syndicated health shows, nationwide. Collaborations are being explored for the future to expand the venues (grocery stores, for example) in which these segments are aired.
- National 5 A Day Week is an annual promotional event that occurs in September of every year. This promotion provides an opportunity to reframe the 5 A Day message in light of emerging research, and reinvigorate program partnerships. Each year, NCI develops and distributes a variety of materials for the media, for the program's state coordinators, and industry partners for their local 5 A Day Week efforts.
- Another effective means to maintain the continued presence of the 5 A Day message has been the extremely successful seasonal outreach media package. Seasonal media promotions are produced twice a year, each reaching up to 4-10 million people. The two most recent seasonal promotions were circulated to over 40 million people via all types of media, including print, electronic, and Internet. Future efforts will focus on building new relationships with other forms of media, including minority and interactive media and using celebrity and expert spokespersons to promote the 5 A Day message.

5 A Day program review and transfer of information to other levels of government, non-profit, civic, and other organizations is and ongoing effort at NCI.

- With the completion of the first decade of the 5 A Day Program, it was appropriate to review its history and accomplishments. In September 2001, NCI published the *5 A Day for Better Health Program Monograph* to describe all facets of the program. Now the public/private partnership model can be utilized by public health programs at the community level to reduce the risk of cancer and many other chronic diseases. In November 2000, NCI published the *5 A Day for Better Health Program Evaluation Report*. This report reviews the science underlying the protective role of vegetables and fruit against cancer and evaluates the success and progress of the program. These publications are available from NCI in print and on the Web. http://behavioralresearch.cancer.gov

- The NCI sponsored an evidence-based review, *"Evidence Report on the Efficacy of Interventions to Modify Dietary Behavior Related to Cancer Risk"* on behavioral research related to dietary change. Conducted by the Agency for Healthcare Research and Quality, it presents results from behavioral interventions conducted in schools, healthcare settings, worksites, communities, and other settings. This systematic review, released in June 2001, clarifies the existing knowledge and offers directions for future research. http://www.5aday.gov/

The National 5 A Day Steering Committee's Vision 2004 states that it will have a comprehensive, coordinated national campaign infrastructure that increases fruit and vegetable consumption to 5 servings per day for 75 percent of Americans by 2010. This target is based on goals set forth in Healthy People 2010, a comprehensive set of 10-year national health objectives developed through a public-private effort sponsored by the U.S. Department of Health and Human Services. Currently, as reported in the upcoming NCI publication *Cancer Progress Report 2001*, total average daily servings of fruits and vegetables increased from 4.5 servings in 1989-91 to 4.9 servings in 1994-96. Among racial and ethnic groups, Blacks had 4.5 total servings; Whites and Hispanics, 5; Asian/Pacific Islanders, 5.6; and Native Americans, 6. It is important to note that these data include food items such as French fries that are not part of the 5 A Day serving recommendations.

To oversee future research and communication efforts, NCI has strengthened the public-private partnership exemplified by the 5 A Day program by recruiting an industry leader in health promotion as the full-time Director of 5 A Day. In addition, an Assistant Director and Communications Coordinator were hired in fall 2001. Their efforts will move the 5 A Day for Better Health toward continued development and success.

NCI looks forward to engaging the public health community in the diffusion and dissemination of both the scientific evidence regarding vegetable and fruit consumption, and the 5 A Day public-private partnership model to improve the diets of all Americans. This will reduce their chances of getting many diseases, including cancer.

Item

Lymphoma- The incidence of non-Hodgkin's lymphoma has grown by an estimated 80 percent between 1973 and 1997 and has a survival rate of only 51 percent. The Committee understands that NCI is currently supporting research to identify possible risk factors for non-Hodgkin's lymphoma, including a case control study investigating the role of immune suppression and stimulation in non-Hodgkin's lymphoma incidence. The Committee encourages NCI to make the investigation of risk factors for non-Hodgkin's lymphoma a high priority and evaluate the possibility of a workshop to assess the state of knowledge of the causes of the disease. (p. 59)

Action taken or to be taken

NCI scientists organized the first meeting of the International Consortium of Investigators Working on Non-Hodgkin's Lymphoma Epidemiologic Studies (Interlymph) in November 2001. The Interlymph Consortium is comprised of epidemiologists and related investigators leading

epidemiological studies of NHL which are recently completed, ongoing, or ready to be launched that include questionnaire data and biospecimens. The researchers are discussing ways to collaborate in a variety of different types of joint efforts such as simultaneously submitting papers on the same topic to a single journal, contributing data on specific topics for pooled analyses, and organizing a multistudy investigation of not uncommon genetic polymorphisms or risk factors for rare subtypes of NHL. The researchers aim to utilize uniform histopathologic groupings and overlapping study components to compare specific hypotheses among studies. All of these and additional efforts will enable the researchers to explore new, emerging areas in NHL epidemiologic research.

The incidence of non-Hodgkin's lymphoma (NHL) has increased about 80 percent over the past twenty years. In addition to incidence rates that have risen 3 percent per year in the United States for four decades, mortality from NHL has also risen 1.6 percent, compared with 0.2 percent for all cancers combined. Only a small portion of the increase is attributable to changes in diagnostic practices, AIDS-related cases, and other known causes. An analysis of trends in both sexes and around the world suggests that an etiologic agent has become increasingly prevalent in the general environment.

Clinical investigations that have shown that prognosis of NHL varies according to histology. These findings have led NCI scientists to assess the demographic patterns and trends in population-based rates of different histologic subgroups of NHL. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade, and peripheral T-cell NHL appear to be distinct entities with specific age, sex, racial, temporal, and geographic variations in rates. Future descriptive and analytic investigations will be designed to evaluate NHL risks according to subtypes, defined by new classification criteria.

Epidemiologic research into the etiology of NHL has examined pesticide use, along with a wide range of other possible risk factors. In a case-control study of NHL in the U.S., NCI scientists are measuring pesticide residues in household dusts, serum samples, and tap water, and collecting questionnaire data on the history of residential pesticide use. Farmers exposed to certain pesticides have been shown to have increased risk for developing NHL. The Agricultural Health Study is a major effort designed to evaluate the relationship between pesticides and other agricultural factors and the risk of cancer and other diseases. Enrollment in this study includes about 90,000 men and women from Iowa and North Carolina. In a separate study, preliminary results suggest that farm exposures are more strongly associated with NHL with a t(14,18) translocation than other types of NHL.

To evaluate the influence of organochlorine exposure on risk of NHL, a nested case-control study was conducted within a cohort of nearly 26,000 healthy subjects in western Maryland who provided blood samples in 1974. Serum PCB levels were found to be strongly associated with subsequent risk of developing NHL, and the effect was potentiated by seropositivity for the Epstein-Barr virus early antigen. These observations are being followed-up in similarly designed prospective studies.

Several other projects to evaluate the cancer risk from pesticide exposure are underway. During the past year, analysis of data from case-control studies of non-Hodgkin's lymphoma noted an

association with agricultural use of lindane, but not with DDT. However, another case-control study indicated that chemotherapy for NHL affects blood levels of organochlorines. Because this could result in misclassification of exposure, prospective studies are planned to clarify relationships with NHL risk.

Databases of water contaminants, gathered for routine monitoring purposes, are being used to estimate past exposures via public water supplies to individuals in these case-control studies. Elevated nitrate levels in public drinking water supplies were associated with an increased risk of NHL in Nebraska. This hypothesis is being investigated further in ongoing case-control investigations of non-Hodgkin's lymphoma in Iowa, Seattle, and the Detroit area.

In analyses based on combined data from three case-control studies, no associations were found between NHL and sunlight exposure, occupational physical activity, or tobacco, although a slight excess risk was seen among women smokers. In addition, an ongoing study is investigating the risk of developing NHL from occupational exposures using a national data set from Sweden called the Cancer Environment Register. NCI intramural researchers are also pursuing a past finding of increased risk of lymphatic and hematopoietic cancer among long-term users of dark hair coloring products in a collaborative study of NHL and multiple myeloma conducted with Yale University.

A retrospective cohort study of cancer mortality in 5,300 subjects treated with nasopharyngeal irradiation (radium) during childhood and 5,200 control subjects in the Netherlands revealed excess deaths due to non-Hodgkin's lymphoma, although no excess deaths due to cancers of head and neck were reported.

The role of viruses, including HTLV-I, HHV-6, KSHV and EBV, is also being examined, and immune-related medical conditions and treatments, sunlight exposures, diet, hair dye use and other hypothesized risk factors are being assessed. Analytic approaches to synthesizing data collected from biospecimens, environmental samples, and computer-assisted questionnaires are also under development.

Using the AIDS-Cancer Match Registry study, NCI scientists have also examined the spectrum of tumors related to KSHV infection risk by looking at second cancer risk in persons with Kaposi's sarcoma. Compared with other persons with AIDS, those persons with AIDS-associated Kaposi's sarcoma had higher risk for certain types of NHL. This relationship appears specific, since no association was found between Kaposi's sarcoma and various other hematologic and solid malignancies.

In the mid-1980s, the University of West Indies, Jamaica and two referral general hospitals in Trinidad and Tobago established parallel registries of hematologic malignancies that were used to identify cases for a hospital-based case-control study of NHL. Persons with NHL, particularly T-cell lymphoma, were found to be significantly more likely to be HTLV-I positive. Up to 60-70% of NHL cases in the Caribbean were estimated to be attributable to HTLV-I. Further characterization of adult T-cell leukemia (ATL) was also performed using case data from these registries.

The focus of the first meeting was to develop strategies such as utilizing common histopathological, immunophenotypic, cytogenetic, and molecular classifications among the different epidemiologic studies, developing methodological approaches for evaluating the potential role of viruses and other etiologic factors in case-control studies, exploring collaboratively the role of specific genetic polymorphisms and genetic pathways as these may be etiologically important in NHL, and considering ways to collectively undertake a large study of multiplex families (those with one or more cases of NHL and related lymphoproliferative malignancies and possibly other related cancers in close relatives) identified in several or most of the individual epidemiological studies. Future meetings will continue to develop these ideas, as well as prepare protocols for collaborative efforts on these topics and address other aspects of the epidemiological studies including the occupational data, exposure to solar radiation derived from interview, dietary factors, and other genetic features.

The NCI has a long-standing dedication to research and therapy of lymphomas. New treatment approaches for lymphoma can be grouped into several categories: biological therapies that utilize monoclonal antibodies or vaccines, chemotherapies that target a specific pathway or a particular macromolecule such as a nucleic acid or a protein, and blood or marrow transplantation.

Monoclonal antibodies (Mab) have now been established as an efficacious agent for the treatment of non-Hodgkin's lymphoma (NHL). The antibodies target antigens on B-cells including CD20, CD22 and HLA-DR. Mabs can be used in its naked form or can be conjugated to radioactive isotopes, toxins, chemotherapeutic agents or other proteins such as cytokines to enhance its ability to kill cancer cells. Rituximab, an anti-CD20 antibody, was approved by the FDA in 1997 for low-grade NHL. Newer antibodies include Zevalin, Bexxar, Hu1D10, and epratuzumab. Zevalin and Bexxar are used as anti-CD20 radioimmunoconjugates. Zevalin will soon be approved by the FDA. Epratuzumab is an anti-CD22 antibody and is currently being tested in the clinic. Hu1D10 targets the HLA-DR receptor.

In order to optimize the use of these antibodies, it is important to have a better understanding of their mechanism of action and the mechanisms by which cells become resistant to these biological agents. The NCI is sponsoring research directed at developing surrogate measures of early events in cell signaling induced in B-cell lymphomas that are sensitive or resistant to antibody-mediated effects and evaluating how those signaling events correlate with clinical response to antibody therapy or the development of drug resistance.

Vaccine therapy has also shown considerable promise. Investigators at Stanford University have developed anti-idiotype vaccines composed of the immunoglobulin chains made by each B cell lymphoma.. The on-going clinical trial in patients in first or best remission after standard chemotherapy involves the immunization of these patients with a vaccine made from the immunoglobulin protein derived from their own tumor. Current efforts also involve new vaccine formulations involving different immunologic adjuvants. In addition, other vaccine strategies will be tested clinically ranging from naked DNA vaccines to immunostimulatory molecules fused onto DNA or protein vectors for introduction to dendritic cells.

Adoptive immunotherapy for the treatment of post-transplant lymphoproliferative disease is another area of special interest to the NCI. Viral specific cytotoxic T cells are used as

prophylaxis against EBV lymphomas. Donor leukocyte infusions are also used for post-transplant lymphoma..

The NCI intramural clinical research program is studying new treatment for AIDS-related lymphoma (ARL). ARL have a poor prognosis, and most people die within one year of developing lymphoma. The NCI has developed a novel treatment approach using a new chemotherapy called EPOCH in combination with the discontinuation of all antiretroviral drugs. The EPOCH chemotherapy may represent a major advance in treatment because it is highly effective in lymphomas and preserves immune function, which is damaged by the HIV virus. There is evidence that antiretroviral drugs may reduce the effectiveness of chemotherapy, but there is concern that the HIV infection will significantly worsen during treatment and lead to early patient death. Thus, the NCI undertook a study of EPOCH chemotherapy in patients with ARL, and carefully evaluated the effect of stopping the antiretroviral drugs on immune function and the HIV infection. This study has recently been completed in 39 patients, and has shown that 77% achieve complete remissions and 63% of patients are alive without lymphoma at over 3 years. Furthermore, the treatment did not cause any long term damage to the immune system or the HIV infection. Hence, this strategy may represent a major medical advance in the treatment of ARL.

More than 80% of patients with follicular NHL overexpress the bcl-2 gene. The product of this gene inhibits apoptosis, or programmed cell death of the malignant lymphocytes which causes the tumors to grow and to be resistant to chemotherapy agents. A new anti-sense compound is in clinical trials which has bcl-2 as its target. Preliminary data suggest that it may be particularly effective when combined with chemotherapy.

The NCI is also involved in the development of a large number of new chemotherapy agents with unique molecular targets or unique mechanisms of action. Drugs which induce apoptosis include compound 506U78, a purine analogue which has demonstrated impressive activity in a variety of lymphoid malignancies, even after failure from bone marrow transplantation, retinoids, and arsenicals. Other agents inhibit the cell cycle including UCN-01, rapamycin, and flavopiridol, or inhibit expression of normal genes through histone deacetylation, such as depsipeptide. Proteasome inhibitors and antiangiogenesis agents are also in clinical trials. Targretin (bexarotene) capsules from Ligand Pharmaceuticals Inc. received approval on December 29, 1999 for the treatment of cutaneous manifestations of cutaneious T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

The role of stem cell transplantation in the management of patients with NHL varies with the tumor histology. Autologous stem cell transplantation clearly benefits patients in a chemotherapy-sensitive relapse of aggressive NHL, but its role as initial treatment is undefined. A National trial is comparing the efficacy of initial transplantation with transplantation at the time of first relapse. Other studies are evaluating the role of biological therapies such as interleukin-2 and rituximab for their effectiveness in enhancing the benefit of transplantation.

Allogeneic BMT may cure patients who cannot be salvaged with standard chemotherapy. However, the mortality of this procedure in patients with lymphomas has been very high. Investigators at the Fred Hutchinson Cancer Center have developed a non-myeloablative

transplant procedure with donor leukocyte infusions in NHL. They have described their experience with patients over the age of 55 years. Graft versus host disease was less than expected and many patients were able to go through the procedure without requiring hospitalization. As a consequence, the notion that more intensive treatment is better is being challenged and the role of the immune system in cancer progression is being better delineated. The group at MD Anderson Cancer Center has used a non-myeloablative regimen of fluadarabine and cyclophosphamide to treat low-grade lymphoma patients who had failed to respond or had a recurrence of disease after initial chemotherapy. Twelve consecutive low-grade lymphoma patients achieved durable complete remissions with no transplant-related mortality. Although promising, long term efficacy of this non-myeloablative transplant procedure remains to be determined and controlled trials comparing this approach to conventional ablative transplant regimens are needed.

The NCI had initiated a comprehensive review of the blood cancers program. The review process invited outside experts to review progress, the current state of science, and resource allocation to a variety of blood cancers. In May 2001, the LLM PRG was convened. The report from this PRG is now available as a hard copy as well as on the NCI web site (http://cancer.gov). Since May, the Institute has carefully reviewed its LLM research portfolio to identify possible gaps and needs that are consistent with the recommendations of the Report. In November, 2001 the Institute convened a meeting of the PRG to discuss the reommendations in the report and to identify strategies to close these gaps. Closing these gaps will be the Insttitute's priority for LLM research. The NCI is now prepararing a plan for implementing the strategies identified at this meeting. The plan will be created by a working group of experts from across the Institute. This group will remain in place to oversee implementation and track progress. Once completed, the plan will be aggressively promoted to the scientific community and to patient advocates. The Institute also will use the plan to prepare a progress report and budget plan for the Committee to review at the FY 2003 appropriations hearings.

Item

Multiple Myeloma- Multiple myeloma is unique among all cancers in that the progress of the disease can be tracked from its precursor through active stages through markers of abnormal proteins in the blood and urine. The Committee urges NCI to collaborate with NIAMS and NHLBI and expand knowledge of these markers through all available mechanisms, as appropriate, including greater use of translational research activities. The Committee also urges NCI to work with CDC regarding epidemiological data gathering and interpretation. (p. 59)

Action taken or to be taken

The NCI remains committed to improving the outcome of patients with multiple myeloma and related diseases through funding basic and clinical research projects. In May 2001, the NCI Director had convened the LLM PRG to sharpen the focus of research programs with respect to hematologic malignancies. The overall goal of the LLM PRG is to develop a national research agenda that prioritizes research questions that will need to be addressed to make progress in leukemia, lymphoma, and myeloma. Members of the LLM PRG, representing basic and clinical researchers from academia, industry, and government, and representatives of the patient

advocacy community, have developed a broad, multidisciplinary research plan. The LLM PRG report has been published (**http://cancer.gov**). Since May, the Institute has carefully reviewed its LLM research portfolio to identify possible gaps and needs that are consistent with the recommendations of the Report. In November 2001, the Institute convened a meeting of the PRG to discuss the reommendations in the report and to identify strategies to close these gaps. Closing these gaps will be the Insttitute's priority for LLM research. The NCI is now prepararing a plan for implementing the strategies identified at this meeting. The plan will be created by a working group of experts from across the Institute. This group will remain in place to oversee implementation and track progress. Once completed, the plan will be aggressively promoted to the scientific community and to patient advocates.

In addition, NCI staff organized a workshop entitled "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities," was focused exclusively on bone microenvironment and metastasis. The workshop covered three major cancers metastatic breast and prostate cancer, and myeloma. The workshop, which brought together scientists and clinicians working in various areas related to bone biology, provided a comprehensive picture of the complex extracellular matrix of the bone and identified potential mediators of cancer cell metastasis. The discussions in the workshop covered these major areas: i) an understanding of the unique features of the bone and its microenvironment that render it an attractive site for tumor cells; ii) ideal experimental models that were useful in studying bone metastasis; and iii) possible targets in the bone that could be used in directing therapy once metastasis has occurred.

Multiple myeloma is the second fastest growing hematological cancer in the U.S. Common effects of the cancer include bone destruction caused by the plasma-cell tumors, life-threatening bacterial infections, and kidney damage. While there has been progress in managing the effects of the disease, conventional chemotherapy has not been successful in treating the underlying cancer. High-dose therapy with bone marrow transplant is used in the management of patients under age 70. However, recent important advances have been made in our understanding of the biology of this disease as well as in the treatment of these patients.

The etiology of multiple myeloma remains unknown. Possible etiologic factors include ionizing radiation, occupational exposures and viral infection. Recent epidemiologic studies have failed to support past associations between benzene and multiple myeloma. However, there is a consistently recognized increase in incidence among agricultural workers. Hormonal influences may also be important, and there are studies underway exploring possible genetic links, as well as past history of inflammatory diseases. While some groups have reported the presence of the human herpesvirus-8 (HHV-8) in the genetic material of stromal bone marrow cells of patients with multiple myeloma, this finding has not been replicated.

NCI investigators collaborated with investigators at Emory University, Medical University of South Carolina, Michigan State University, Karmanos Cancer Institute, and the New Jersey State Health Department in a case-control study conducted in Atlanta, Detroit, and New Jersey to examine possible reasons for the excess of multiple myeloma in the black population. Findings from this study highlighted low occupation-based socioeconomic status (SES), low education and low annual family income as risk factors that could account for a substantial amount of the black/white differential in the incidence of multiple myeloma.

Another analysis from this study found elevated risks associated with obesity, while reduced risks were related to eating cruciferous vegetables and fish and taking vitamin supplements, particularly vitamin C. The greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may explain part of the higher incidence of multiple myeloma among blacks compared to whites in the United States. This study also investigated myeloma risk associated with diagnostic x-ray exposure. However, no increased risk was observed. NCI investigators are continuing their efforts to explore other risk factors associated with the race-related difference in incidence rates for multiple myeloma.

Overt myeloma is often preceded by a disorder known as Monoclonal Gammopathy of Undetermined Significance (MGUS). The group from the Mayo Clinic is evaluating the prevalence of this entity by measuring specific abnormal protein markers in the blood and urine and is following these patients to determine the frequency with which multiple myeloma develops and the immunological changes which may be associated with this transformation. These investigators have devised an assay that potentially can differentiate patients that will progress from MGUS to multiple myeloma from those who will not. This assay is based on the different roles played by IL-1-beta and IL-6 in the growth of myeloma cells. IL-1-beta is secreted by patient's bone marrow cells and IL-1-beta induces IL-6 production in neighboring stromal cells. IL-1-beta is also abnormally produced in all patients with myeloma. Thus the amount of IL-6 produced by stromal cells incubated with bone marrow culture supernants from patients can be used to distinguish between MGUS and active multiple myeloma.

This observation has led to the filing of a patent using IL-1-beta inhibitors for the treatment of multiple myeloma. The rationale behind this treatment approach is that IL-1-beta plays an important intermediary role in IL-6 production which is required for the growth of myeloma cells. Inhibition of IL-1-beta will lead to inhibition of IL-6 production which in turn will result in inhibition of growth of myeloma. This new treatment strategy uses information learned about the tumor microenvironment as well as cell-cell interactions. Other cytokines that are being evaluated in this setting include IL-4 and IL-12.

Several laboratories have demonstrated increased density of blood vessels in the bone marrow from patients with multiple myeloma, suggesting abnormal angiogenesis. As a result there is great interest in evaluating new antiangiogenesis agents in this disease. A number of protocols are determining the activity of these agents along with chemotherapy or stem cell transplantation. Mayo clinic investigators are assessing changes in bone marrow angiogenesis, expression of a number of angiogenic factors and their receptors before, during and after thalidomide therapy to determine how best to use antiangiogenesis therapy.

BCNU is an agent with demonstrated activity in multiple myeloma. Unfortunately, the cells eventually become resistant because of the activity of a number of cellular mechanisms. These include (1) reduced intracellular drug accumulation, (2) alterations in the drug target that reduce drug-induced damage, (3) repair of drug-induced damage, and (4) inhibition of programmed cell death pathways.

NCI has been focusing on a molecular targeted approach toward drug development particularly agents that involve programmed cell death pathways. These include the proteosome inhibitor

PS-341, the BCR-ABL tyrosine kinase inhibitor, STI571 and farnesyl transferase inhibitors, R115777 and BMS214662. At the American Society of Hematology meetings in December 2001, Millenium Pharmaceuticals reported a highly positive result from a multi-institutional Phase II clinical trial on multiple myeloma patients that were treated with PS-341.

High dose chemotherapy with autologous stem cell transplantation has emerged as a standard treatment option with multiple myeloma. Data on more than 1,500 consecutive patients, either newly diagnosed or with limited prior treatment, treated at a single center indicate that up to 50% can achieve complete remission and responses can be sustained for 10 years and longer in those patients lacking chromosome 13 deletion, presenting with low beta2-microglobulin and low C-reactive protein. Nevertheless, few, if any, patients are cured with this procedure. As a result a number of modifications are being evaluated, including the addition of drugs such as thalidomide.

Allogeneic bone marrow transplantation remains the only potentially curative therapy for multiple myeloma . However, the toxicities associated with this procedure in patients with multiple myeloma have been almost prohibitive, with a 30%-50% treatment-related death rate. Moreover, age restrictions limit the number of patients who might be eligible for this conventional transplant procedure. Investigators from the Fred Hutchinson Cancer Center have devised a non-myeloablative transplant procedure, "mini-transplant procedure" for patients over 55 years of age. They have shown that this mini-transplant procedure is well tolerated and can be performed on an out-patient basis. Mini-transplants with donor leukocyte infusions were adopted in the setting of post-thalidomide relapses at the University of Arkansas. Complete responses and near complete responses were observed in 8 of 16 patients. Patients with chromosome 13 deletions who underwent mini-allogeneic transplants after one preceding auto-transplant also had a 50% response rate (complete response or near complete response).

Despite these new transplant procedures, many patients still fail stem cell transplantation. Major efforts are directed at identifying the reasons for failure and to develop methods to improve on these results. Investigators at a number institutions are developing anti-myeloma specific T cells to treat minimal residual disease following transplantation. Other investigators are taking a gene therapy approach, transducing donor lymphocytes with a suicide gene that will permit the infused lymphocytes to have the beneficial graft-versus-myeloma effect but without the graft versus host disease.

The NCI also funds the International Bone Marrow Transplant Registry which is the world's largest body of data on outcomes following transplantation for myeloma and other tumors. Data is provided from more than 400 centers and there are now data for more than 65000 transplants world-wide. These data are used for determining transplant regimens for specific clinical situations, identifying prognostic factors, comparing transplant regimens, comparing transplant with non-transplant approaches, evaluating cost and cost-effectiveness, planning clinical trials, and developing approaches to evaluate patient outcome.

Often the major feature of multiple myeloma is skeletal pain from compression fractures or pathologic fractures from increased osteoclastic bone resorption. Bisphosphonates, analogues of

endogenous pyrophosphates in our bodies, are potent inhibitors of bone resorption. This class of compounds is used to treat/palliate myeloma.

Newer more potent derivatives of bisphosphonates, the aminobisphosphates (ibandronate and zoledronic acid) are in active clinical trials. Zometa (zoledronic acid) from Novartis Pharmaceuticals Corporation, received approval on August 20, 2001, for the treatment of hypercalcemia of malignancy. A number of other types of anti-bone resorptive agents are entering early clinical trials including integrin inhibitors, osteoprotegerin, and anti-parathryoid-related peptide antibodies.

Investigators at University of Tennessee Medical Center are tackling a group of related diseases to multiple myeloma that is associated with disorders of the human immunoglobulin light-chain. These include myeloma (cast) nephopathy (MCN), light chain deposition disease (LCDD) and light-chain associated (AL) amyloidosis. All three disorders involve the deposition of specific marker monoclonal light chains in organs. The Southwest Oncology Group has initiated a novel Phase II clinical trial for patients with AL amyloidosis using 4'-iodo-4'deoxydoxorubicin (I-DOX). This is the first national cooperative group clinical trial in this disease. It turns out that I-DOX in certain patients can cause the resorption of amyloid deposits.

Item

Natural Products Drug Development.--The Committee encourages NCI to enhance the Natural Products Drug Development program, particularly in the area of complementary and alternative medicine. Recent surveys indicate that a majority of cancer patients will include complementary and alternative therapies in their treatment regime. NCI is encouraged to support high quality research proposals investigating cancer therapies such as iscadore and other botanical substances. Ayurvedic, homeopathic, traditional Chinese approaches, and alternative dietary approaches. The Director of the Institute should be prepared to provide a progress report at the fiscal year 2003 appropriations hearings. (p.59)

Action taken or to be taken

The NCI's Developmental Therapeutics Program, Office of Cancer Complementary and Alternative Medicine (in collaboration with the National Center for Complementary and Alternative Medicine), Natural Products Branch, and Division of Cancer Prevention each support high quality research projects as specified below:

The Developmental Therapeutics Program of the NCI manages a Natural Products Research Program consisting of several components:

Extramural contracts and collaborations for collection of plants and marine organisms:

- Three new plant collection contracts have been awarded for working in Africa *(Madagascar - 500 samples/year)*, Southeast Asia *(Bangladesh, Cambodia, Laos, Vietnam - 500 samples/year)* and the United States, including Hawaii and U.S. Territories *(1,000 samples/year)*.

- 1 marine organism collection contract working in Micronesia, South Africa and New Zealand.
- 20 collaborative agreements (Australia, Papua New Guinea, Bangladesh, China, Korea, Costa Rica, Brazil, Fiji, Iceland, Mexico, New Zealand, Pakistan, Panama, and South Africa).
- Collections are performed in close collaboration with source country scientists, and voucher specimens of every organism collected within their borders are donated to its national repository. Countries only receive data for those organisms collected within their borders. Scientists keep data confidential until NCI pursues isolation studies to determine the potential for patenting. Agreements and Letters of Collection are in place to respect the rights of the source countries.

On-site repository, extraction and screening of natural product extracts:

- The Natural Products Repository is located at the NCI-Frederick Cancer Research and Development Center.
- The Natural Products Extraction Laboratory prepares raw materials from the field (e.g., leaves, bark, twigs) into extracts which can be tested by in vitro and in vivo systems.
- Currently the repository contains over 150,000 extracts. On average, an additional 5,000 extracts are added to the repository each year.
- The Developmental Therapeutics Program In Vitro Cell Line Screening Program tests extracts from the repository against human tumor cell lines. Extracts which meet minimum testing levels are provided to U.S. investigators through the Active Repository Program for study as a source of new anticancer agents.
- The Open Repository Program provides samples of extracts from the repository as a resource to research investigators world-wide for testing against any human disease. Since 1992, 44 organizations have had access to the Program, including the U.S. Army (USAMRIID) who are testing for inhibitors of bioterrorism agents including anthrax and other bacterial toxins.

The NCI also supports grant programs such as the Natural Product National Cooperative Drug Discovery Groups (NP NCDDGs), International Cooperative Biodiversity Groups (ICBGs), and other investigator-initiated grants (R01s, R29s, etc.)

Item

Neurofibromatosis- The Committee encourages NCI to strengthen its neurofibromatosis (NF) research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation and clinical trials through all available mechanisms, as appropriate. The Committee also urges NCI to continue to coordinate its efforts with other Institutes engaged in NF research. (p. 59)

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. Because NF may affect cognitive functions as well as hearing and sight, these disorders fall within the purview of a

number of institutes within NIH, and attempts are being made to coordinate the research effort across NIH. NCI efforts continue to build upon the workshop last year hosted by NINDS to assess the status of NF research and to identify future research opportunities. Several priorities were agreed upon at the workshop, including development of more refined animal models for NF1 and NF2; further analysis of the mechanisms of action of neurofibromin and merlin - the proteins whose functions are disrupted in NF1 and NF2 respectively; and the identification of modifier genes that affect the expression of neurofibromin and merlin.

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 NF may exist, but are not yet fully characterized. At least 85 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 percent. In both major forms of NF, severity of symptoms can vary greatly. Effects can be severely disabling, mildly disfiguring or can even go undetected.

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.

Recently a more targeted approach for the treatment of progressive plexiform neurofibromas has become available and is being studied. The underlying cause of NF1 is a defective gene. The function of this gene is to produce a protein called neurofibromin. In patients with NF1, neurofibromin is decreased, and the decrease in neurofibromin is felt to contribute directly to tumor formation. Neurofibromin helps control the activity of another protein called *ras*. *Ras* can be thought of as an "on/off" switch for cell growth. When *ras* is "on", cells divide. When *ras* is "off", the cells do not divide. Neurofibromin helps to keep *ras* turned "off". Decreased levels of neurofibromin therefore may allow for uncontrolled cell division and tumor formation. Drugs that inactivate *ras* are being studied as a new way to treat cancer. These drugs may also provide a logical means of controlling the tumors in patients with NF1.

One class of drugs that inhibits *ras* signaling is the farnesyl-protein transferase (FTase) inhibitors, and the NCI is supporting Phase I and Phase II trials of drugs in this class for the treatment of solid tumors and leukemias in both adults and children. The NCI has initiated accrual to a clinical trial studying the FTase inhibitor R115777 for patients with NF1 who have progressive plexiform neurofibromas. This important study will determine whether R115777 can slow the time to disease progression for patients with progressive plexiform neurofibromas and will determine whether R115777 can make plexiform neurofibromas decrease in size.

NCI also supports clinical trials through the pediatric clinical trials cooperative groups that specifically include children with cancers associated with NF1. Of special concern are the brain tumors associated with NF1 and in particular the low-grade gliomas that develop in children with NF1. The Children's Oncology Group continues accrual to its clinical trial (CCG-9952) for children younger than 10 years of age with progressive low grade astrocytoma. Approximately 200 children have now been entered into this study, and at current rates of accrual, the study should complete patient enrollment in two years. 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.

NCI Intramural scientists began studies of neurofibromatosis 2 (NF2) in 1987. This disorder is characterized by development of bilateral vestibular schwannomas (VS; Schwann cell tumors of the vestibular branch of the 8th cranial nerve), which cause hearing loss and vestibular symptoms in early adulthood. Meningiomas and other benign central and peripheral nervous system tumors are also common. Although neurofibromatosis 2 is relatively rare, unilateral vestibular schwannomas and meningiomas comprise 30% of all brain tumors in adults. The study population has consisted of two major groups: members of multi-generation multiplex neurofibromatosis 2 families, and sporadic cases whose parents are unaffected clinically. Patients with neurofibromatosis 2 and their at-risk relatives undergo a detailed clinical evaluation that includes gadolinium-enhanced MRI of the brain (and the spine in affected individuals), ophthalmologic, and audiologic examinations, a physical examination that includes evaluation of cranial and spinal nerve function, and giving a blood sample for molecular genetic studies.

DNA from the largest family in the study (11 affected individuals in three generations) contributed to the fine mapping of the NF2 gene to a small region of the long arm of chromosome 22. A few years later, DNA from affected individuals in this family was found to have a 234 base pair deletion in a candidate gene cloned from this region. The deletion was not present in any unaffected family members; its co-segregation with disease in this family confirmed that the gene containing the deletion was indeed the NF2 gene.

In addition, intramural clinical studies demonstrated a new feature of neurofibromatosis 2, the presence of two different types of cataracts at an early age. They also suggested that two major subtypes of neurofibromatosis 2 families exist. Patients with severe disease usually develop symptoms before age 20, have many central nervous system tumors in addition to vestibular schwannomas, and rapid clinical progression. In contrast, patients with mild disease often are symptom-free until the third decade of life and have few tumors other than vestibular schwannomas. In general, affected family members have similar manifestations. To date, 20 different NF2 germline mutations have been identified in 21 of our neurofibromatosis 2 families. By comparing the clinical and molecular data in these families, the phenotypic manifestations have been shown to correlate strongly with type of mutation. Mutations that shorten the C-terminus of the NF2 protein usually result in severe neurofibromatosis 2, whereas mutations

that replace one amino acid with another usually lead to mild disease. Moreover, mutations that alter intron splicing result in variable phenotypes even within members of the same family. NCI Intramural investigators have begun collaborating with extramural investigators to refine the understanding of genotype-phenotype correlations, and to examine the natural history of neurofibromatosis 2, beginning with vestibular schwannomas and spinal tumors.

In this regard, NCI Intramural investigators have recently completed a study examining factors that influence the rate of growth of the vestibular schwannomas (VS) in NF2 patients. In general, VS growth rates were found to be highly variable, but tended to decrease with increasing age at onset of signs or symptoms of NF2, and age at diagnosis of NF2 (e.g., the VS in patients who were older when they first had symptoms of NF2 or were diagnosed with NF2 tended to have slower growth rates than those in patients who were younger when they first had signs of or were diagnosed with NF2). The rate of growth of the VS was not influenced by either the type of NF2 mutation that the patients had, or by the presence in the patients of other cranial or spinal tumors. Finally, the observed growth rates of VS were found to be highly variable among affected relatives of similar ages from the same family. The implication of this finding is that the clinical course and approach to management of VS in one family member is not likely to be useful in predicting the clinical course or best approach to management of VS in other family members, even when other clinical aspects of NF2 may be similar.

Significant progress has been made in the development of animal models for NF. 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. 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 percent 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.

Item

Ovarian Cancer- Ovarian cancer remains one of the deadliest cancers for women, in part due to the lack of effective early screening methods. The Committee urges NCI to expedite current research in screening methods to detect, diagnose, and identify staging of ovarian cancer. The

Committee also encourages NCI to fully fund the four ovarian cancer SPOREs and accelerate research in this area through all available mechanisms, as appropriate, including the establishment of additional ovarian cancer SPOREs. (p. 60)

Action taken or to be taken

In February 2001, the NCI convened a Gynecologic Cancer PRG to identify and prioritize those areas of research that held the best promise for advancing progress in ovarian, cervical, and endometrial cancer. A roundtable meeting of approximately 120 experts in related fields was held in June , 2001. The recommendations of the PRG were officially accepted by the NCI in December, 2001. Several of the highest priorities identified by the PRG concerned ovarian cancer. These included the elaboration of a specimen resource, the identification of precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indications, and new targets for prevention and treatment, as well as efforts to eliminate disparities in care and improve patients' quality of life. As with PRGs in other cancer sites, the NCI has convened a trans-institute working group to implement the recommendations.

Ovarian cancer incidence and mortality rates have declined among U.S. Women age 35-59 years during the period 1970-1995. Epidemiologic studies have shown that ovarian cancer risk decreases with increasing parity and increasing duration of oral contraceptive use. During this period, parity declined while oral contraceptive use increased. NCI Intramural scientists compared temporal trends in observed ovarian cancer incidence rates with rates predicted by changes in parity and duration of oral contraceptive use to determine whether the changes in these characteristics could explain the declining rates in younger women. In addition, oral contraceptive use was examined to see if it continues to be protective to postmenopausal women. The predicted rates agreed well with observed rates in young women (age 30-49) but were substantially lower than observed rates in older women (age 50-64). The data indicated that the relative decrease in incidence rates due to the protective effect of oral contraceptive use declines with age.

A large case-control study in Poland of breast, endometrial and ovarian cancers is currently underway to evaluate the interrelationship of genetic and environmental factors. This study has special components to assess the relationship to cancer risk of occupational exposures (given that a large proportion of Polish women work outside their homes, often in industrialized settings) and of physical activity (women are being asked to wear accelerometers to provide more objective evidence of their recreational, occupational and household levels of physical activity). This study also has an extensive pathologic component in order to allow precise classification of tumors and to assess the influence of various tumor markers, including some of which are being assessed by newly developed tissue microarray techniques.

Several NCI-sponsored clinical studies are poised to accrue women at high risk of developing ovarian cancer to interventions with chemopreventive potential. One of these studies is being conducted by the Gynecologic Oncology Group (GOG) and a second by a consortium of investigators. Both clinical studies are designed to assess the impact of chemopreventive agents on biomarkers generated by or related to characteristics of the ovarian epithelium. The women participating in these studies have decided to obtain prophylactic oophorectomy on the basis of a

strong family history or other evidence of a genetic mutation known to confer ovarian cancer risk. The agents under study are the oral contraceptive pill and a Vitamin A-like compound, 4 hydroxyphenyl retinamide.

The NCI's PLCO trial, which recently completed accrual of 146,000 men and women, included an evaluation of serum CA 125 and ultrasound as screens for ovarian cancer. Investigators associated with the PLCO study obtained early results by analyzing the baseline transvaginal ultrasound examination results for 20,000 postmenopausal women. In this group of asymptomatic women, ovarian abnormalities identified on ultrasound were assessed for their potential to be ovarian cancer precursors by correlating them with known ovarian cancer risk factors. Several strong risk factors for ovarian cancer such as a family history of ovarian cancer or breast and ovarian cancer and long term oral contraceptive use were not associated with the presence of complex cysts, simple cysts, bilateral cysts, or all abnormalities combined. These observations suggest that the abnormalities found on ultrasound were not immediate precursors of ovarian cancer.

The Ovarian Cancer Early Detection Proteomics Initiative is a component of the Clinical Proteomics Program, an inter-agency collaboration between the Center for Cancer Research, NCI and the Center for Biologics Evaluation and Research, Food and Drug Administration (FDA). The mission of this new initiative is to credential and validate a new proteomics/bioinformatics technology that has preliminarily demonstrated high sensitivity, specificity, and positive predictive value for the discrimination of the presence of ovarian cancer, including stage I, from benign ovarian disease and unaffected women. This test, using less than a drop of serum, involves making a protein fingerprint of 15,500 proteins in the low molecular weight protein range. This fingerprint is then analyzed using a pre-trained multi-dimensional pattern discovery algorithm. This system correctly identified all cancers, including all stage I cancers in the test sets. This approach is easily applied to point of care and it is envisioned that it can be applied broadly through secure web links; it is estimated that the cost per test per patient will be less than $100.

A second initiative in the Ovarian Cancer Project of the Clinical Proteomics Program, NCI/FDA, is global unbiased protein target and marker discovery directly from patient specimens. This project applies state of the art proteomic technology to protein pattern analysis, protein isolation, and micro-sequencing for identification. This project has identified and attributed selectively to invasive ovarian cancer over a dozen new or known proteins. Ongoing work is validating these findings for use as new molecular treatment and/or imaging targets.

Over the last year the NCI has opened numerous clinical trials for women addressed at prevention, screening and treatment of ovarian cancer. These trials include the following:

- Screening and Prophylactic Surgery in Women at Inherited Risk of Ovarian Cancer: Among the many pressing clinical issues in the management of women who carry mutations in BRCA1/2 is the optimal screening strategy as well as the appropriate role of prophylactic oophorectomy as a risk reduction strategy. The NCI's Cancer Genetics Network (CGN) has just opened a large screening trial in which women who elect to retain their ovaries will be monitored with a novel ovarian cancer screening algorithm based on the rate-of-change of CA125 levels over time. Data from this study will be

pooled with data from a similar trial underway in the United Kingdom. In addition, the US study, conducted in partnership with NCI intramural investigators and investigators from the Gynecologic Oncology Group (GOG) will also evaluate the impact of prophylactic oophorectomy. The following issues will be addressed: (a) what is the prevalence of clinically occult ovarian cancer at the time of prophylactic oophorectomy? (b) are there identifiable precursor lesions in the ovaries of genetically at-risk women? (c) what is the incidence of primary peritoneal carcinomatosis and breast cancer subsequent to this operation? and (d) how does this surgical procedure affect the quality of life for the women who elect it?

- New Drugs and Combinations for Women with Advanced Ovarian Cancer: In January, 2001, the NCI, working through the Gynecologic Oncology Group, initiated a new trial evaluating the role of three new drugs, gemcitabine, topotecan, and liposomal doxorubicin in conjunction with two standard chemotherapy agents, platinum and paclitaxel, for women diagnosed with advanced ovarian cancer. This trial, which seeks to build upon the improved survival noted with the addition of paclitaxel, will be the largest Phase III treatment trial conducted to date among women with ovarian cancer. The NCI has worked closely with US investigators to develop collaboration with investigators in Australia, Great Britain, Italy, and New Zealand for this trial, so that the trial will accrue the required number of patients as quickly as possible. In addition, the NCI has worked closely with the Ovarian Cancer National Alliance to develop patient information material for this trial and to promote accrual to the trial.
- Phase II Clinical Trial with Proteomic Profiling of Imatinib Mesilate (Gleevec), A PDGER and C-KIT Inhibitor, in Patients with Refractory or Relapsed Epithelial Ovarian Cancer: This clinical trial is the first to evaluate both the clinical and biochemical activity of a molecularly targeted agent, such as the tyrosine kinase inhibitor, imatinib mesilate (Gleevec), in patients. Patients will receive imatinib mesilate twice daily in treatment of their tumor. Biopsies of a sentinel tumor mass will be taken prior to treatment and after one month of treatment. Tumor cells will be microdissected using the NCI Laser Capture Microdissection system and then applied to NCI/FDA Clinical Proteomics Program tissue lysate arrays for direct comparison of the activity of key signal transduction proteins prior to and during drug treatment. This will allow analysis of multiple pathways important in ovarian cancer and of how successfully they are being affected in the tumor in the patient. This clinical trial is designed uniquely to determine if the agent is effective and how.
- Cancer Vaccine Therapy with Tumor Specific P53 Peptides for Patients with Low Burden Adenocarcinoma of the Ovary: This trial is the first to test the ability of a cancer vaccine to prevent recurrence of ovarian cancer in patients who have completed standard therapy and currently have no evidence of disease. The vaccine is directed against the individual's mutant p53 protein. At least fifty percent of epithelial ovarian tumors carry an abnormal p53 protein. The aim of this study is to generate an immune response against the abnormal p53 protein that will focus on the tumor cells and not normal cells. Outcome markers are development of an immune response to the vaccine and duration of disease-free period.
- Treatment Results from Ongoing Research: The NCI, working through the Southwest Oncology Group and Gynecologic Oncology Group, recently found that paclitaxel given over many months (17-20 months) helped women to live longer than paclitaxel given for

a shorter period (8-11 months). Paclitaxel, a drug developed by the NCI, had been given on the same schedule as platinum, generally every 3-4 weeks for 6-8 treatments. This new study suggests that long-term administration of paclitaxel may help women with ovarian cancer live longer than ever before.

Over the last year, the NCI has worked to build infrastructure to support ovarian cancer research, both in the extramural community and within the intramural programs at the NIH. As of FY 2001, the four ongoing SPOREs in Ovarian Cancer are fully funded. These four SPOREs have also recently decided to participate in a high risk screening trial for ovarian cancer through a collaboration with the NCI-sponsored Cancer Genetics Network (CGN). The trial involves the monitoring of quarterly CA125 levels and the performance of annual transvaginal ultrasounds (TVS) on high risk women. The primary objective of this pilot study is to test the efficacy of obtaining periodic CA125 values and to determine if this screening method, along with TVS, is effective in detecting ovarian cancer at an earlier time point in these women. This pilot study will provide additional information and may be the basis for a larger and more comprehensive screening trial in high risk women for ovarian cancer.

A critical mass of researchers in the Center for Cancer Research and the Division of Cancer Epidemiology and Genetics dedicated to clinical, translational, population, and basic science research into the gynecologic cancers has formed the NCI Gynecologic Oncology Faculty. The mission of the gynecologic Oncology Faculty is to promote interactions between basic, population, translational and clinical researchers with interests in gynecologic malignancies. These interactions will advance understanding of the molecular etiology, cell biology, epidemiology, prevention and treatment of gynecologic malignancies and to explore new opportunities. The Faculty will interact with the extramural gynecologic and general research communities, local practice colleagues, academia, and industry and will partner with the ovarian cancer advocacy movement. The Faculty will reach out to the gynecologic cancer patient community, and their families and caregivers. The Faculty contains the following areas of excellence: population science; immunology and vaccines; proteomics, transcriptomics and genetics; invasion and angiogenesis, radiation oncology and imaging, and clinical trials development and execution.

Immediate action items of the Faculty include sponsorship of an open workshop to develop and validate a consensus epidemiologic tool for assessment of risk for all gynecologic cancers. This tool will then be applied to new protocols and will be applied to the ongoing Ovarian Cancer Early Detection Proteomics Initiative. A second workshop, in partnership with the Clinical Proteomics Program, will determine optimal methods for tissue collection and use for early detection, prevention, and clinical trials programs. A targeted objective of the faculty will be to develop an educational program for community.

Item

Primary Immune Deficiency Diseases- A symposium held in March 2000 to investigate the relationship between primary immune deficiency diseases and cancer showed that primary immunodeficiency patients have a 200 times greater risk of developing cancer than someone without primary immunodeficiency. The Committee encourages NCI to develop a

comprehensive research portfolio in this area. The Director of the Institute should be prepared to provide a progress report at the fiscal year 2003 appropriations hearing. NCI is also encouraged to expand its role in a national education and awareness campaign through all available mechanisms, as appropriate. (p. 60)

Action taken or to be taken

The NCI is interested in the relation between primary immune deficiency diseases (PID) and cancer. Statistical data indicates that individuals with PID show a 100-200 fold increase risk in developing cancer. In addition, there is a higher incidence of some cancers in minority populations. The data suggests that these minority individuals may have some form of undiagnosed PID. This information was presented for discussion at a meeting on PID and cancer held in March 2000. One of the results of that meeting was an emphasis to further studies on PID and cancer in minority populations. Recently, NCI and NIAID began a research agenda by co-funding a study to assess PID and cancer in children of under-served populations. The focus of these initial studies is to screen, diagnose, and treat PID in these children and ultimately decrease their risk of developing cancer.

Currently NCI, NIAID, and NICHD are cofunding an R18 grant entitled "Targeting Primary Immunodeficiency Diseases in Minority Populations". The hypothesis is that PIDs occurs much more frequently in minority populations than the data suggests (data shows much lower prevalence than in Caucasians) and is being under-diagnosed in these populations because physicians and other health care workers are unaware of these diseases in minority populations. The grant is to develop a new screening method based on a combination of classifications which will be prospectively validated in several New York city hospitals. There is also a large education component aimed at health care providers of minorities primarily Hispanic and African-American populations. The data collected from these studies will be utilized to focus research on PID and cancer in these and other minority populations.

In addition, NCI program staff plus the Acting Director of NCI met with the Jeffrey Modell Foundation co-founders in October, 2001. The purpose of the meeting was to coordinate NCI efforts in alerting the cancer biomedical community to the prevalence of PID in minority populations. These efforts will also provide additional data on the prevalence of cancers in minority populations particularly those diagnosed with PID. As a result, NCI will include a link to the Jeffrey Modell Foundation website on the NCI website. This will provide further education to the cancer biomedical community of the importance of diagnosing PID and cancer in minority populations. Still in the planning stage, the collaborative effort will focus on the underserved populations with educational materials printed in both English and Spanish. Heightened awareness, prompt treatment, and improved medical surveillance will likely reduce the incidence of cancer in these patients.

Item

Prostate Cancer- Cancer of the prostate is the most commonly diagnosed non-skin cancer in America and tends to disproportionately affect men who are members of minority groups. 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 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 result in earlier, more reliable detection methods and more effective and less disfiguring treatment regimes. (p. 60)

Action taken or to be taken

Prostate cancer is the single most common form of non-skin cancer in men in the United States. In the year 2001, an estimated 198,100 men will be diagnosed with prostate cancer, and some 31,500 will die of the disease. It is however a very heterogeneous disease with an extremely varied clinical course, which complicates clinical decision making. Furthermore, although very substantial progress has been made within the last few years in understanding the biology of prostate cancer, there is still much to learn with regard to its causation, the reasons for its heterogeneity, and how it may be prevented.

NCI's prostate cancer research is guided by the 1998 recommendations of the Prostate Cancer PRG. Through the PRG process, NCI invited researchers, clinicians, advocates, and patients to review the NCI research portfolio and develop a national research agenda for prostate cancer by identifying new or unmet scientific opportunities to hasten progress against the disease. At an implementation meeting with the PRG in January of 1999, the NCI Director proposed a series of actions in response to the Prostate PRG recommendations. The results of the PRG recommendations and implementation then served as the basis for developing a 5-Year Plan (Planning for Prostate Cancer Research: Five Year Professional Judgment Estimates) presented to Congress in June 1999.

NCI is committed to reporting on progress in addressing the recommendations of the PRGs that have been convened for various types of cancer. As envisioned in 1999, a process to report progress relevant to the Prostate Cancer PRG has been initiated. An internal working group of prostate cancer experts has been assembled and is in the process of choosing measures of progress, collecting data, and preparing a progress report. When the progress report is complete, a group including some former Prostate Cancer PRG members will meet to review progress and recommend any adjustments to NCI strategies. These recommendations will be used in the formulation of the revised prostate research plan for FY 2003 - 2008 that will be submitted to Congress by April 1st, 2002.

Some of the major domains of current research are: etiology and epidemiology (understanding the causes of prostate cancer and factors that may alter its prevalence); fundamental biology; therapy; and prevention research. Important etiologic clues include geographic, environmental, racial, dietary, hormonal, behavioral, and other differences in prostate cancer risk.

Although African Americans have the highest reported incidence of prostate cancer in the world, the burden of this disease in Africa is largely unknown. Because Africans and African Americans share similar genetic ancestry yet have vastly different lifestyles, a better understanding of the rates and risk factors for prostate cancer among Africans will provide

important etiologic clues to the relative roles of lifestyle and genetic factors, as well as their interplay, in prostate cancer risk. NCI scientists are initiating a new study of prostate cancer in Ghana to fill this important knowledge gap.

Another major population study is underway in Shanghai, China, an area where the reported incidence for clinical prostate cancer has been the lowest in the world, but has started to rise rapidly. Results thus far demonstrate a relationship between higher levels of insulin and insulin-like growth factor I (IGF-1), and lower serum levels of IGF binding proteins, with a significantly increased risk. Analyses are correlating serum levels of hormones, IGFs, insulin, and leptin with anthropometric factors and physical activity, which may shed light on hormonal and other mechanisms of prostate carcinogenesis.

This is just one line of research that points to the complex and presumably crucial linkages between prostate cancer and hormonal differences. The role of several genetic markers involved in the regulation and metabolism of androgens is being assessed, including the androgen receptor (*AR*) and the steroid 5 alpha-reductase type II (*SRD5A2*). NCI scientists are also investigating polymorphisms of hormone-related genes, .molecular studies of pathways related to insulin, such as the obesity-sex-hormone pathway, potential cross-talk between the IGF, the vitamin D receptor (VDR), and the insulin-signaling pathways, and the relationships between serum and prostate tissue hormonal levels.

Other studies are investigating the frequency of several potential prostate (and other) cancer susceptibility genes. The search is made difficult because of the diversity and the late onset of this disease, which often precludes the examination of large families in which all members are currently alive. The International Consortium for Prostate Cancer Genetics (ICPCG) was formed in 1996 to address and overcome through collaborative research the problems associated with prostate cancer susceptibility gene mapping and identification. Currently, this consortium consists of over 25 institutions in 7 different countries in North America, Europe and Australia, all of whom already have ongoing research programs in this area. Together, this group has collected DNA samples from over 1,400 prostate cancer families, making this combined resource unique, and by far the largest one of its kind. A published study of 772 families showed stronger evidence of linkage to the already identified HPC1 locus in families with male-to-male transmission, with earlier mean age at diagnosis and multiple members affected. The size and diversity of this group, including families from diverse ethnic and racial groups, makes it ideally suited to address questions pertinent to the molecular genetics and genetic epidemiology of prostate cancer. In addition, this collaborative infrastructure would make it possible to expeditiously address other crucial questions when prostate cancer genes are cloned, such as gene frequency and penetrance, clinical correlations, and implications for genetic testing.

At that point it will coordinate with the NCI's Cancer Genetics Network (CGN), an established national network of 8 major centers specializing in the study of inherited predisposition to all types of cancer. The CGN supports collaborative investigations on: the genetic basis of cancer susceptibility, mechanisms to integrate this new knowledge into medical practice, and means of addressing the associated psychosocial, ethical, legal, and health issues. In 1999, pilot research in prostate cancer gene discovery was initiated within the CGN, focusing on the recruitment of

prostate cancer patients and their relatives, and persons who may be at increased risk of developing prostate cancer.

Gene discovery research is also being performed by, among others, the International Consortium for Prostate Cancer Genetics (ICPCG) and the Specialized Programs of Research Excellence (SPORE) for prostate cancer. The prostate cancer SPOREs were developed to promote interdisciplinary research and to speed the bidirectional exchange between basic and clinical science in order to move basic research findings from the laboratory to applied settings involving prostate cancer patients and populations.

It should not be concluded, however, that genetic and racial factors account for the entirety of the observed risk differences. Data from migration and other studies suggest a role for environmental factors in promoting late-stage disease. Among those for which there is preliminary evidence of relevance are chronic inflammation as a result of increased oxidative stress related to higher fat intake, increased alcohol consumption, and possibly a sexually transmissible agent.

In order to improve understanding of the environmental and genetic determinants of this disease, an NCI-sponsored workshop entitled "Emerging Opportunities in Prostate Cancer Epidemiology" was held in October 2000 to bring together leading epidemiologists, geneticists, molecular biologists, and pathologists and there will be a need for similar symposia in the future,

Over the last several years, and in response to recommendations by the Prostate Cancer PRG and interest in Congress, the scope of NCI drug development for prostate cancer has grown several fold. The number of NCI-funded prostate cancer clinical trials ongoing at any one time is now in the range of 250-300 Phase I, II, and III studies, making it one of the most active segments of the clinical trials portfolio. Prostate cancer trials are now the second most active research area for the NCI's large national Cooperative Groups. Also, as presented in the 5-year plan, an effort is being made to find a way to study in prostate cancer virtually every new agent that is developed under NCI auspices. This process has been accelerated by NCI efforts to establish common standards and methods for such research. Furthermore, these efforts and especially the enhanced public visibility of prostate cancer research efforts have made this disease a frequent focus for drug development by private industry.

A broad array of clinical trials are underway that explore new agents alone or in combinations with other treatments in advanced cancers, but there has also been a major effort in the last 2-3 years to expand research into treatment testing in the adjuvant therapy setting (where treatments are intended to prevent recurrence after primary surgical or radiation treatment) and in the setting of rising PSA levels as the only indicator of disease after definitive local therapy. Among the most promising new approaches currently under study are molecularly targeted agents that interfere with the expression of key genes involved with prostate cancers and other malignancies such as receptor tyrosine kinases, cox-2, and genes in the cell death pathways. Also, many studies involve inhibitors of angiogenesis (tumor blood vessel formation) and metastasis (tumor spread to other organs). These agents are specifically designed to attack the establishment of prostate cancer metastases in bones, a promising strategy only feasible now because of improved understanding of the biology of metastasis and development of new types of drugs. NCI also has

an extensive program of investigation of immunologic approaches to prostate cancer, including a number of vaccine strategies targeting PSA, PMSA and other markers expressed by these tumors, and utilizing various approaches to stimulating an effective immune response.

Another major component of NCI's commitment to accelerating progress in prostate cancer research is the SPOREs program (Specialized Programs of Research Excellence). This was expanded from three to now eight major academic centers of excellence that are working on a wide range of scientific approaches focused on translational research – that is, focusing on the biology of prostate cancer specifically as it may be useful in developing new treatments (and on how treatment effects can be improved by gathering information about the biology). These eight SPORE programs are also developing projects that they will carry out collaboratively.

NCI also has a pair of highly successful programs, the RAID and RAPID programs, intended to expedite new agent development on the part of independent investigators in universities or in small or medium size biotechnology companies. This is done by making NCI's preclinical drug development resources and expertise available for moving novel molecules toward clinical trials. Rapid Access to Intervention Development (RAID) and Rapid Access to Prevention Intervention Development (RAIPID) have been previously described to Congress. Those selected for support are assisted with necessary development steps to enable Investigational New Drug Application (IND) filing with the FDA and to begin initiation of proof-of-principle clinical trials. The investigators are then free to develop industry collaborations in whatever way that suits them. The RAID program is currently supporting 4 such agents being developed specifically for prostate cancer.

Following the successful enrollment of over 18,000 patients in the first ever major trial of chemoprevention in prostate cancer, NCI has just launched the second generation prevention study, the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial), which will enroll 32,000 men and will serve as a major test of dietary supplementation to reduce the risk of prostate cancer development in moderate-to-high risk individuals.

In addition, NCI is 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. NCI-supported investigators have developed a set of human prostate cancer xenograft models known as LAPC for Los Angeles Prostate Cancer. These models can be used to study the transition from androgen dependence to androgen independence, as well as the process of metastasis following orthotopic injection. Using such models they have uncovered a role of a tumor suppressor gene, PTEN in prostate cancer. Since this protein negatively regulates an important cell survival pathway (the PI3-kinase/Akt pathway), human prostate cancers lacking PTEN showed elevated activation of this survival pathway. Enhanced Akt pathway also provides a novel therapeutic target to control the growth of prostate cancer.

Also using the PTEN approach, another group of investigators has designed a genetic mouse model which lacks two important proteins (PTEN and p27). Absence of these two proteins results in spontaneous neoplastic transformation and incidence of tumors in various organ systems including breast and prostate. The prostate cancers seen in these mice recapitulate the natural history and pathological features of human prostate cancer.

In a better refinement of the TRAMP model, NCI-supported investigators have developed another genetic model of prostate cancer. This prostate cancer model goes a step further in demonstrating hormone-independent growth that occurs with the failure of androgen-ablation therapy. An added advantage of this mouse model would be that it permits an analysis of sequential genetic changes that occur during the multi step process in prostate carcinogenesis.

Also, two important studies by NCI supported investigators are focused on establishing models of prostate cancer that metastasize to the bone. In one model human bone is transplanted into the hind limbs of mice which are immuno-compromised. When human prostate cancer cells are injected into these mice, the cancer cells home only to the human bone and do not colonize the mouse (host) bone. In the second model, investigators first isolated a special cell line from the ascitic fluid of a patient with advanced prostate cancer. This cell line, ARCaP (Androgen Repressed Cancer of the Prostate) when administered orthotopically, metastasizes to a number of organs, including the lymph nodes and skeleton. This model has two unique features: (a) it exhibits a metastatic pattern similar to what is seen in human prostate cancer patients, and (b) it recapitulates the antiandrogen withdrawal syndrome where tumors regress transiently but grow again and become resistant to hormone therapy. Together, these models will permit a better understanding about the biological interaction between human prostate cancer cells and bone and may enhance our understanding of the events associated with prostate cancer metastasis to the bone.

The foregoing discussion has focused on finding new therapies. When it comes, though, to assessing not brand new treatments, but the relative efficacy of established approaches, a different set of research strategy is helpful. The kinds of randomized trials that could clarify the relative efficacy of alternative types of treatment for early stage prostate cancer (radiation therapy, brachytherapy, radical prostatectomy, androgen deprivation therapy, or watchful waiting) are not easy ones for men to consider thoughtfully when they have just been stressed by a new diagnosis of cancer and have therefore been difficult to complete. Moreover, certain treatments can have different detrimental effects on urinary, bowel, and sexual functions. To date, there have been no accurate estimates of the changes in functional status among men treated in everyday community settings. More than 80 percent of men diagnosed with prostate cancer have clinically localized prostate cancer.

The Prostate Cancer Outcomes Study (PCOS) was initiated in 1994 to look at the impact of treatments for primary prostate cancer on long-term complications and the quality of life of patients. One of the unique features of this study is that the participants represent a large community-based group of patients treated in all types of health care settings, with a substantial number of minority men. By collecting patient survey data on the health outcomes of various treatments for prostate cancer, the PCOS will help patients, their families, and physicians make more informed choices about treatment alternatives.

PCOS investigators have found that among patients with clinically localized cancer, men receiving radical prostatectomy were more likely than those receiving radiotherapy to be incontinent (10% versus 4%) and to have higher rates of impotence (80% vs. 62%), although large, statistically significant declines in sexual function were observed in both treatment groups. Men undergoing radiotherapy reported greater declines in bowel function than did men receiving

radical prostatectomy. These estimates of long-term treatment complications are much higher than estimates from previous studies conducted in major academic medical centers.

Other PCOS-based studies have reported on health outcomes following radical prostatectomy, the value of diagnostic imaging studies, and the probability of pathologically advanced disease among men undergoing radical prostatectomy for suspected early stage disease. Other published studies have reported on complications following radiation therapy and hormonal therapies, and the contribution of sociodemographic and clinical factors to population patterns of treatments used for early stage prostate cancer. For more information about the PCOS, visit http://appliedresearch.cancer.gov/PCOS/results.html

SEER data show that African Americans have about twice the risk of non-Hispanic whites of being diagnosed with advanced stages of prostate cancer (12.3% vs. 6.3%), while Hispanics are intermediate (10.5%). Socioeconomic status, clinical and pathological factors each contributed to the increased risk. After adjusting for other clinical and sociodemographic variables, the risk remained significantly higher for African Americans. This research helps to clarify health disparities by race and ethnicity by focusing on the role played by socioeconomic factors. Among men who had not completed high school or lacked private insurance, African Americans and Hispanics were more likely to present with APC. With higher socioeconomic status, the difference for African Americans persisted but disappeared for Hispanics. Thus, the increased risk observed for African Americans could not be explained fully by looking at household income, employment status, educational level, and insurance status. This suggests that either this widely used constellation of socioeconomic factors may not sufficiently describe the disparities in access to and use of health care or that biologic factors may have a role. Ultimately, efforts to reduce prostate cancer mortality in African Americans should incorporate the racial disparity in clinical stage at diagnosis. Further research should be directed at the identification of biologic markers and genetic susceptibility factors, as well as socioeconomic factors including use of health care systems, distance from health care, diet, literacy, and health beliefs.

Item

[National 5 A Day for Better Health Program] **--** The Committee is aware of the Report of the Evaluation Group on the national 5 A Day for Better Health Program. Given the report's favorable evaluation of the program, the Committee urges the Department of Health and Human Services (HHS) to strengthen and expand the 5 A Day program and develop a comprehensive plan to promote better health through increased consumption of fruits and vegetables. The Committee recognizes the importance of the public/private partnerships that have made the 5 A Day program so successful and expects that future efforts by CDC and NCI to expand the 5 A Day program will continue to involve these partners. (p. 60)

Action taken or to be taken

Please refer to pages NCI-54 through NCI-56 of this document for NCI's response to this significant item regarding National 5 A Day for Better Health Program.

FY 2002 Senate Appropriations Committee Report Language (S. Rpt.107-84)

Item

Blood Cancers – The Committee is interested in NCI's upcoming Progress Review Group report on leukemia, lymphoma, and multiple myeloma, and it is eager to know what research strategies NCI is pursuing to improve treatments for these blood cancers. In particular, the Committee urges NCI to expand its research on myelodysplasia, a serious blood disorder affecting primarily older adults and individuals who have previously undergone radiation or chemotherapy treatment for cancer. The Committee has listened to testimony about the devastating effects that multiple myeloma has on its victims and recognizes that, despite recent advances, median survival for patients responding to treatment is only 3 to 5 years. The Committee urges continued research and effort to seek new and better treatment for this disease. The Committee also requests that the NCI and NIEHS develop a joint report by April 1, 2002, on the progress of lymphoma and hematological cancer research. The report should address how the PRG has determined funds will be expended to expand the current base of lymphoma and hematological cancer research. (p. 120)

Action taken or to be taken

Please refer to pages NCI-39 through NCI-44 of this document for NCI's response to this significant item regarding Blood Cancers.

Item

Brain Tumors – The Committee is concerned that insufficient attention is being given by NCI and the National Institute for Neurological Diseases and Stroke (NINDS) to brain tumor research. The recently issued report of the NCI/NINDS-sponsored Brain Tumor PRG has called for substantially greater effort into this little-understood area of tumor research and treatment. The Committee encourages NCI to fund at least three Specialized Program of Research Excellence in Brain Tumors (SPORE) grants in the upcoming fiscal year, with particular emphasis on those proposals which include both basic research and clinical treatment applications. (p. 121)

Action taken or to be taken

Brain tumors are a serious problem in both children and adults, though the specific types of tumors are quite different in these two age groups. For adults with brain tumors, high-grade astrocytomas predominate, and 5-year survival rates are quite poor, especially for persons diagnosed at age 65 years and older. Mortality rates for adults with brain tumors have shown little change over the past 20 years. For children, a number of different types of brain tumors occur, including ependymoma, medulloblastoma, low-grade astrocytomas, high-grade gliomas (both supratentorial and in the brain stem), and atypical teratoid/rhabdoid tumors. Prognosis varies from very good for children with some types of low-grade astrocytomas, to very poor for children with brain stem gliomas and atypical teratoid/rhabdoid tumors. Overall 5-year survival

rates for children with brain tumors have risen to approximately 69%, and there has been a modest decline in childhood brain tumor mortality rates since 1975 (~25% decline).
NCI continues to focus attention on brain cancer research. Future planning for brain tumor research activities builds upon the recommendations of the Brain Tumor PRG. These recommendations are directed across the range of scientific opportunities, from the basic biology of normal and cancerous brain cell growth and survival, to epidemiological and animal modeling studies to identify genetic and environmental factors associated with brain cancer development, to research evaluating new treatment approaches for children and adults with brain cancers. These efforts will be coordinated with NINDS through an NCI/NINDS brain tumor working group that will meet on a quarterly basis.

NCI over the past 5 years has emphasized the development of brain tumor consortia – networks of neuro-oncology centers of excellence. Two such consortia have been funded to focus primarily on adult high-grade gliomas. The program has been operational now for about 4 years and currently involves 19 centers throughout the US. Their cumulative research agendas now involve over 30 clinical trials, and they are capable of completing 8-10 studies per year. A third consortium, the Pediatric Brain Tumor Consortium (PBTC) focuses on childhood brain tumors and has been operational for more than 2 years. The activities of these consortia are described below.

NCI has solicited applications for brain tumor "Specialized Programs of Research Excellence" (SPORE) grants. Six applications were received and will be peer-reviewed early in 2002. The NCI plans to fund brain tumor SPOREs based on the scientific merit of the applications as assessed by the reviewers' recommendations and based on the availability of funds.

In addition to the extramural activities of the brain tumor consortia, NCI and NINDS intramural researchers have established the intramural Neuro-Oncology Branch, a collaborative, joint effort by the NCI and NINDS to develop novel diagnostic and therapeutics for children and adults with brain and spinal cord tumors. Intramural investigators from the Pediatric Oncology Branch are also conducting Phase I studies evaluating new agents for children with brain tumors.

The two adult brain tumor consortia, the "New Approaches to Brain Tumor Therapy" (NABTT) and the "North American Brain Tumor Consortium" (NABTC), have markedly expanded the clinical research agenda for therapy of gliomas in adults. They have successfully evaluated the efficacy and pharmacokinetics of NCI sponsored agents and have incorporated molecular and biological analyses into clinical trials of novel agents aimed at specific molecular targets. Both consortia have established strategic collaborations with industry sponsors, which is important as these sponsors have the largest portfolio of novel agents. Because the consortia can complete studies more efficiently than any single cancer center or company and can perform types of clinical research that would be difficult in less specialized networks such as Cooperative Groups, the consortia have become the primary focus nationally for most new agent trials in adult brain tumors. Between 1998-2000, the two consortia enrolled a total of 1013 patients in onto approximately 30 Phase I and Phase II trials. From 1998 through early 2001, the consortia produced 98 publications, manuscripts, or abstracts and presentations.

Several general themes have come to occupy a substantial proportion of the and research strategies of the two consortia:

Receptor tyrosine kinases and signaling pathways as molecular targets in brain tumor therapy. These signaling pathways control cancer cell growth and survival, and inhibitors of these pathways can have potent anti-cancer activity. Specific agents/pathways that have been studied include:

- STI-571 (Gleevec), which is an inhibitor of the platelet-derived growth factor receptor and the c-Kit receptor;
- ZD1839 (Iressa) and OSI-774, which are inhibitors of the epidermal growth factor receptor;
- R115777, a farnesyl transferase inhibitor. The NABTC Phase II trial of R115777 demonstrated a substantial rate of objective response and a high rate of disease stabilizations in patients with recurrent high-grade gliomas; and
- CCI-779, which inhibits the mTOR protein, a protein that has multiple effects in stimulating tumor cell growth and survival.

Optimizing the locoregional components of brain tumor therapy:

- An important area of research is the identification of new agents that enhance the anti-cancer activity of radiation therapy. New types of radioenhancing compounds such as RSR-13 and gadolinium texaphyrin have been studied by the adult consortia. Plans are in place to study other agents with potential radioenhancing activity, including phenylbutyrate and COX-2 inhibitors;
- Consortia trials have demonstrated that five-fold higher local exposures of the chemotherapy agent BCNU are possible with an investigational formulation of Gliadel (BCNU intratumoral wafers). Consortia investigators are trying to further enhance the activity of the Gliadel wafers by use of O^6-benzylguanine (O^6BG), an inhibitor of O^6-alkylguanine-DNA alkyltransferase (AGT) that is a key cause of BCNU-resistance in gliomas;
- NABTT studied Gliasite, a temporarily implantable balloon reservoir that permits ^{125}I solution brachytherapy into a brain tumor resection cavity. This device won approval from FDA entirely on the basis of the NABTT study;
- Other novel locoregional therapies include regional administration of new agents, especially biologics, via convection-enhanced delivery; and
- The adult consortia have instituted important clinical trials of gene-based therapies, including the Onyx-015 agent (a genetically modified virus designed to replicate in cancer cells with mutant p53) and Introgen's AdP53 system.

Angiogenesis as a therapeutic target: Because of the high vascularity of glioblastomas, anti-angiogenic agents have been prioritized for evaluation by the adult consortia. The consortia have studied the following compounds:

- Thalidomide as a single agent and thalidomide given in combination with temozolomide;
- SU5416, a small molecule inhibitor of one of the receptors for vascular endothelial growth factor (VEGF);
- Col-3, a matrix metalloproteinase inhibitor; and

- EMD 121974, an anti-angiogenesis agent that inhibits integrin-mediated signaling leading to death of some tumor blood vessel cells.

A major thrust for both adult consortia has been integrating the evaluation and analysis of relevant molecular and biological markers into clinical studies. One way to make this feasible is to incorporate administration of an agent for a short period prior to resection of the tumor to allow detailed tumor tissue studies. With this approach, information is obtained on whether an agent is altering the putative target within the tumor, in addition to data on clinical outcome and pharmacokinetics. For example:

- The dose of O^6BG to be used in subsequent studies was not determined by toxicity or plasma concentrations, but rather by measurement of brain tumor AGT levels to establish the administered dose that actually achieved *in vivo* 99% inhibition of enzyme activity.
- The Gleevec (STI571) trial included evaluation of key proximal and downstream molecular targets for Gleevec to determine whether the dose of Gleevec used was actually able to modulate these targets in tumor tissue.
- The Phase I adeno p53 clinical trial evaluated p53 status, gene transfer levels, apoptotic index and p21/p16 in resected tumor tissue.

The RFA for the adult brain tumor consortium effort will be re-issued in FY 2002 with the intention of funding this effort for a further 5 years. A major change, however, will be the integration of resources for research in neuroimaging. These additional resources are provided so that the brain tumor consortia can assist in identifying non-invasive imaging techniques that can determine whether or not a novel agent is actually altering its intended molecular target within a brain tumor. Such a strategy was recommended by the Brain Tumor PRG and if successful would represent a very powerful tool in speeding the selection and development of promising new approaches to the therapy of brain tumors.

The Pediatric Brain Tumor Consortium (PBTC) and the Children's Oncology Group (COG) are the primary mechanisms by which the NCI supports clinical research for children with brain tumors. The PBTC is beginning its third year and is serving as an important vehicle for the introduction of new therapeutic approaches into the pediatric population. Because the number of children with brain tumors is much smaller than the number of adults with brain tumors and because the types of brain tumors in children are quite different from those of adults, the research program of the PBTC differs from that of the adult brain tumor consortia both in magnitude and in the types of studies prioritized. Among the clinical challenges facing the PBTC and the PBTC response to these challenges are the following:

- Improving outcome for young children with brain tumors, for whom outcome is poor and for whom treatment-related sequelae (largely from radiation) may be devastating. The PBTC-001 study is addressing this challenge by evaluating the experimental intrathecal agent mafosfamide given in combination with an intensive systemic chemotherapy regimen and with conformal radiation. The hypothesis is that the intrathecal chemotherapy, which is delivered directly into the cerebrospinal fluid, may reduce the need for radiation therapy, with its associated neurological side effects, for these young children. The PBTC is also studying the intrathecal administration of the chemotherapy agent busulfan.

- Children with brain stem gliomas have very low survival rates. The PBTC-006 study is evaluating whether Gleevec (STI571), an inhibitor of the platelet-derived growth factor receptor, can be safely given to children with brain stem gliomas in combination with radiation therapy and following radiation therapy. The study will also obtain preliminary evidence of whether Gleevec given in this manner improves outcome for children with brain stem gliomas. The PBTC-007 study is using a similar design to determine whether Iressa (ZD1839), an inhibitor of the epidermal growth factor receptor, can be safely given with radiation for children with brain stem gliomas.
- For all types of childhood brain tumors, new treatment approaches are needed, and the PBTC is evaluating new classes of anti-cancer agents to determine how they can be safely administered to children with brain tumors. Anti-angiogenic therapy is a promising strategy, and the PBTC-002 study is evaluating the VEGF receptor inhibitor, SU5416. The farnesyl transferase inhibitor Sch66336 is also being studied by the PBTC.
- New approaches to providing local therapy for children with brain tumors are an important priority for the PBTC. The PBTC will begin in 2002 a study evaluating the ability of O^6-benzylguanine (O^6BG), a systemic inhibitor of O^6-alkylguanine-DNA alkyltransferase (AGT, a key mechanism of BCNU-resistance in gliomas) to enhance the activity of Gliadel (BCNU-impregnated wafers) implanted in the tumor resection cavity. The PBTC also plans to open in 2002 at least one study evaluating intratumoral administration of a toxin-conjugated molecule that binds to brain tumor cells.
- The PBTC is also evaluating O^6BG given in combination with temozolomide, as AGT is also a major mechanism of resistance to temozolomide.

The PBTC is pioneering efforts within the cancer clinical research community to establish centralized image collection and analysis for multi-institutional consortia. The PBTC Neuroimaging Center has been established at Duke University, in collaboration with the Resource Center for Emerging Technologies (RCET) at the University of Florida. Mechanisms have been developed for electronic transfer of imaging data from PBTC institutions to the Neuroimaging Center. The electronic transfer of protocol-related imaging studies is a key infrastructure component of the PBTC's ability to conduct state-of-the-art clinical research for children with brain tumors. This capability will be critical in allowing the PBTC to take advantage of novel non-invasive methods for evaluating the effects of targeted anti-cancer agents on tumor tissue.

The COG Brain Tumor Committee is another important NCI-supported activity for children with brain tumors and primarily focuses on the development of Phase II trials (in collaboration with the COG Developmental Therapeutics Committee) and the development of Phase III trials.

- For children with ependymoma, the most important predictor of survival is whether or not the tumor is completely resected. COG is evaluating the ability of chemotherapy to allow complete tumor resection for those children whose tumors were not resectable at their first surgery. The study is also evaluating the role of conformal radiation therapy for children with ependymoma, since more focused radiation may reduce damage to normal brain tissue and diminish long term side effects of therapy.
- For children with high-grade astrocytomas, COG is conducting a study to determine whether temozolomide given during radiation therapy and after the completion of radiation therapy results in an improvement in event-free survival.

- For children with medulloblastoma, a major concern is the long-term sequelae associated with radiation to the entire spine and brain (craniospinal radiation). COG is planning studies to begin in 2002 that will attempt to reduce radiation damage without compromising outcome by either dose reduction of craniospinal radiation or by the use of conformal radiation to focus on the tumor while minimizing radiation dose to normal adjacent tissues.

Another important focus of the COG Brain Tumor Committee is the identification of biological markers of tumor behavior that will allow risk-based stratification of childhood brain tumors, risk-adapted therapy, and eventually therapy that is targeted to biological targets present in specific tumor types. COG investigators determined that children with high-grade gliomas whose tumors have mutations in the p53 tumor suppressor gene have worse outcome than children whose tumors have normal p53. In other work, COG investigators demonstrated that among young children with primitive neuroectodermal tumors of the brain, those who have atypical teratoid/rhabdoid tumors (AT/RT) have significantly worse outcome. A diagnosis of AT/RT can now be identified by detection of mutation in the *Ini1* gene within tumor tissue. Ongoing work from tissue specimens collected from a recent medulloblastoma study is attempting to confirm preliminary results that expression of TrkC (a nerve growth factor receptor) is associated with favorable outcome for children with medulloblastoma. If confirmed, future studies will stratify patients on the basis of whether their tumors express TrkC (more favorable outcome) or do not express TrkC (less favorable outcome requiring more aggressive therapy).

The etiology of brain tumors is poorly understood. Data from the NCI SEER Program (Cancer Statistics Review, 1973-98) show that brain tumor incidence increased from 1973 to 1990 at an annual rate of 1.3%, and from 1991 to 1998 declined at a rate of 1.3%. Whether the earlier increase was, in part, real or is entirely an artifact of improved diagnosis is a controversial issue. Nonetheless, concern has arisen that one or more increasingly common environmental exposures might cause brain cancer. Fxamples include industrial chemicals, pesticides, food additives, and electromagnetic fields. In response to such concerns, and to advance understanding of environmental, behavioral and genetic causes of brain tumors, NCI Intramural scientists have collaborated with investigators at three U.S. Hospitals to conduct a case-control study of malignant and benign brain tumors. Factors under consideration include workplace exposures to chemical agents and electromagnetic fields, use of cellular telephones, dietary factors, family history of tumors, genetic determinants of susceptibility, reproductive history and hormonal exposures, medical and dental exposure to ionizing radiation, other aspects of medical history and home appliance use and hair dyes. Key features of the study include its large size, the emphasis on rapid ascertainment of incident cases and interview of study subjects rather than surrogate respondents, and the use of detailed, job-specific questions developed by industrial hygienists to ascertain occupational exposures. Blood samples were collected for genetic and mutagen sensitivity studies. At present, DNA extracted from the blood samples is being evaluated to determine whether brain tumor cases differ from controls in the frequency of polymorphisms of the glutathione transferase family of genes, and polymorphisms of other metabolic genes. The first report from this study concerned use of cellular telephones. Cell phone use did not increase the risk of brain tumors, even among people who used one for more than 60 minutes per day or for five years or more, nor did tumors occur more often on the side of

the head on which a phone was used. Risk of glioma was significantly reduced among persons with a history of allergies or autoimmune disease.

As a follow-up to the comprehensive case-control study of adults with brain tumors described above, a family-based study of the parents, siblings and adult children of the 480 eligible glioma cases identified in the case-control study is being conducted by NCI Intramural investigators. Relatives are interviewed about personal and family medical history. Medical and risk factor information including environmental and occupational exposures will be collected from them as well as buccal (mouth) cells, as a source of DNA. When the data collection from this study is complete, intramural scientists will repeat the analyses done in the original case-control study, but use relatives as controls. Of special interest will be association studies of common polymorphisms in genes for enzymes that metabolize drugs and carcinogens, and mutations in other candidate genes. Use of related controls in these analyses will ameliorate concerns about the potential bias that could result from comparing cases with unrelated controls drawn from populations that differ genetically from the cases for the disease and genetic variables of interest.

Once established, this case-control family study will be a unique resource for other types of analyses designed to elucidate the role of genetic and environmental factors in the etiology of gliomas. Complex segregation analyses can be used to model genetic and environmental influences, including effects from a single major gene, as well as effects from many genes, each having small effects (polygenes). If statistical analyses of verified cancers in first-degree relatives of the glioma cases suggest an excess of any cancer or group of cancers, and segregation analysis suggests that the pattern of occurrence of the excess cancer(s) is consistent with transmission of a single gene, we will extend the data collection efforts to second- and third-degree relatives in the families with the cancers of interest and obtain blood samples for gene mapping studies.
NCI Intramural Investigators recently completed case-control studies of cancers of the brain in Nebraska farmers that will provide the opportunity to assess the role of agricultural, general environmental, and lifestyle factors in the development of these tumors. Blood and urine have been collected from 30 applicators applying the herbicide 2,4-D to relate dose to possible biologic effects, and dose-response gradient was found for 2,4D and mitotic index.

An evaluation of new cancers in 28,884 allogeneic bone marrow transplant recipients demonstrated an increased risk of solid tumors, with the cumulative incidence reaching 8.1% ±± 3.1% at 20 years post-transplant. Compared to an age and sex matched general population, transplant recipients were at significantly higher 2.3-fold risk of developing a new invasive solid cancer and a 6-fold increased risk of brain cancer. Most of the 18 patients who subsequently developed brain cancer had received prior radiation exposure at a young age, either given as cranial irradiation prior to the transplant or transplant conditioning with total body irradiation.

NCI Intramural investigators are conducting studies of multiple primary cancers in persons with brain cancer. Data collected through the Surveillance, Epidemiology and End Results (SEER) program are being used to evaluate the risk of new primary cancers in persons with a first cancer of the brain and nervous system. NCI is collaborating with extramural investigators in a case-control study of brain tumors among childhood cancer survivors. This study is addressing the risk of brain cancer with respect to treatment for the childhood cancer.

NCI Intramural investigators are evaluating the role of nutrition in studies of lung, oral/pharyngeal, esophageal, stomach, colorectal, breast, endometrial, cervical, prostate, and *brain cancers*, as well as non-Hodgkin's lymphoma and malignant melanoma. Research approaches include descriptive analyses to generate hypotheses, analytic cohort and case-control investigations, large-scale nutritional intervention studies (clinical trials), metabolic studies, and biologic marker and genetic susceptibility projects

NCI supports a number of research programs to improve understanding of the biology of brain tumors through molecular characterization of tumors and through the development of animal models of human brain tumors. Relevant programs include:

The Brain Tumor Molecular Anatomy Program (BMAP) is a trans-NIH project aimed at understanding gene expression and function in the nervous system. Its two major scientific goals are gene discovery and gene expression analysis. In pursuit of these goals, BMAP has launched several initiatives to provide resources and funding opportunities for the scientific community. BMAP is also in the process of establishing physical and electronic resources for the community, including repositories of CDNA clones for nervous system genes, and databases of gene expression information for the nervous system. Most BMAP initiatives so far have focused on the mouse as a model species because of the ease of experimental and genetic manipulation of this organism, and because many models of human disease are available in the mouse. However, research in humans, other mammalian species, non-mammalian vertebrates, and invertebrates is also being funded through BMAP.

The Brain Tumor Genome Anatomy Project (BTGAP) is a collaborative effort between NINDS and NCI's Cancer Genome Anatomy Project designed to develop a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy. Currently the focus is on gene expression from specific malignant gliomas and the development of the first glioma chip

Development of Zebrafish Mutagenesis and Screening Tools is a Program Announcement, sponsored by multiple institutions of the NIH, that is intended to encourage investigator-initiated applications for research designed to exploit the power of mutagenesis screening in zebrafish in order to detect and characterize genes, pathways, and phenotypes of interest in development and aging, organ formation, behavior, and disease processes.

The NCI initiated the Mouse Models of Human Cancer Consortium (MMHCC) in September of 1999 to derive or refine mouse cancer models, and explore in depth their correspondence to human cancer. Of the twenty groups in the MMHCC, two have neuro-oncology models as their primary focus, and another, models that are based on the malignancies associated with neurofibromatosis types I and II. In addition, as the investigations in the consortium have proceeded, other groups are discovering that neurological cancers arise in their genetically engineered models. In some cases, the manipulated gene is causally associated with human brain cancer, and so the result is not unexpected. One such example is the *PTEN* gene, alteration of which generates brain tumors in addition to prostate and endometrial and other cancers. Other models are based on alterations of EGF-R, the epidermal growth factor receptor, and on PDGF, or platelet-derived growth factor, yielding mice that develop a variety of tumors whose

characteristics are fairly representative of adult and pediatric brain tumors. In addition, there are instances in which the observation of brain tumors is not anticipated (i.e., the gene has not previously been linked to brain cancer), and these discoveries provide new leads for human disease etiology.

One important goal of the MMHCC is to ensure that the mouse models are used as extensively as possible for translational cancer research. The models are preclinical tools to test clinically relevant hypotheses arising from basic science discovery, as well as to disclose the underlying mechanisms for lack of response to therapy or development of resistance. For example, MMHCC investigators are using a mouse model of oligodendroglioma to test the efficacy of neuronal stem cells to deliver anti-angiogenesis therapy directly to the tumor cells without affecting the surrounding normal cells. In addition to their novel therapeutic approach, these investigators are incorporating MR imaging to follow the delivery of the agent and the subsequent effect on the tumor *in vivo.* Depending on the outcome, tissues from the mice will be assayed for gene expression and histopathology before and after treatment to define what molecular and morphologic changes are associated with positive and negative outcomes. Another MMHCC group is using their glioma and astrocytoma mouse models to test the efficacy of anti-angiogenesis inhibitors that are delivered by adenovirus and adeno-associated virus vectors. In addition, they are testing a new class of therapeutic agents, the histone deacetylase inhibitors, in these same models. Like the studies on the oligodendroglioma model, these investigators employ MR imaging and high-throughput assay methods to analyze the response of the mouse tumors *in vivo* and *in vitro*.

To foster interactions with the pharmaceutical and biotechnology industries, the MMHCC has regular meetings of the NCI-MMHCC Pre-Clinical Trials Roundtable. Working collaboratively with the private sector, interested mouse model researchers are exploring the practical considerations of the use of transgenic mice for drug discovery and testing. In return, the private sector roundtable members make available to the mouse modelers some of their most promising lead compounds to test in the models. The potential of mouse models of all malignancies, including brain cancers, to inform the selection of molecular targets for human therapy or to test agents for their efficacy against particular targets remains insufficiently explored. The NCI recently advertised a program announcement, "Cancer Therapy-related Use of Genetically Engineered Mice" that encourages collaborations between clinicians and developers of such models to explore the appropriate use of them to tackle clinically relevant questions, particularly those that are difficult or impossible to test with human subjects. There are a number of mouse brain tumor models that are well enough characterized to be used for this purpose, and the modelers will be urged to apply to this program.

The previously mentioned oligodendroglioma mouse model is an exceptional resource for defining the ensemble of genes associated with susceptibility to this kind of brain tumor. The patterns of loss and gain of DNA from chromosomes in the mouse oligodendrogliomas correspond to characteristic losses and gains in chromosomes from human tumors. This is promising evidence that the disease in the mice recapitulates the genetic progression of human cancer with sufficient fidelity for further study. In addition, the tumors are highly infiltrating and metastatic, and display the genetic complexity and localization that makes this a good model to understand childhood glioma. The various inbred mouse strains that are genetically engineered

to derive cancer models differ in how susceptible or resistant they are to developing cancer, and this differential susceptibility enables researchers to localize and narrowly refine the responsible regions of the mouse chromosomes. The corresponding locations in human chromosomes are then interrogated for potential polymorphic susceptibility genes. The original oligodendroglioma mouse model has now been crossed with different inbred mouse strains; studies on the resulting mice indicate that there are a number of genes that modify this particular cancer trait, and the investigators are undertaking the search for those genes.

How best to employ the speed and power of mouse genetics and the data and resources of NCI-sponsored epidemiologic studies to accelerate the pace of human susceptibility gene discovery was the subject of a very recent meeting of investigators from the MMHCC and from the NCI's Cancer Genetics Network. The consensus of the group was to assemble cancer-site-specific working groups immediately to catalog the available human resources and tally the relevant mouse models to support common problem solving objectives. Because appropriate brain tumor models are available, the planned collaborations can proceed quickly to identify specific genes. Depending on the biological properties of the available models, the genes identified may contribute to susceptibility, modify the aggressiveness of the tumors, or alter their response to therapy.

Identification of susceptibility genes paves the way to use the mice to study interactions with suspected environmental risk factors. Knowledge of the interplay of genes with the underlying etiologic factors can inform the design and testing of newer brain cancer models to permit identification of early tissue or serum markers that presage cancer development. One group of MMHCC researchers has a promising lead on a small molecule that is secreted by developing astrocytomas; they are using their corresponding mouse model to search for that, and other, secreted molecules in mouse serum. Finding proteins or other small molecules in the usual tiny quantities of mouse blood is a formidable challenge; it has only recently become feasible through application of suitable nanotechnologies. These approaches use nanoliters of mouse blood, permitting researchers to take serial samples of blood from the same mouse and perform clinical tests that parallel those performed on human subjects.

The MMHCC investigators collaborate with the members of the Early Detection Research Network and the Director's Challenge Program to devise and test comparable platforms for high throughput determination of gene and protein expression. The goal of these coordinate activities is to ensure that the analyses of human and mouse cancer proceed in parallel and synergistically, so that discovery in one system informs research in the other. The bioinformatics tools required to support an integrative cancer biology approach are provided by the NCI Center for Bioinformatics. As these programs produce results, the research community will have several Internet gateways to access information according to their interests or needs. These websites will serve not just as a clearinghouse of facts about human and mouse cancer, but also as a tool for scholarly discovery.

The MMHCC is committed to ensuring that information about the latest tools for derivation, characterization, and application of mouse models is widely disseminated. The consortium facilitates many on-going activities related to brain cancers, including convening regular brain cancer models histopathology consensus meetings, sponsorship of mouse models symposia at

national and international neuroscience and neuro-oncology conferences, and support for a project designed to derive terminology concepts that allow integration of mouse and human cancer information to facilitate discovery.

The Neuro-Oncology Models Forum Program includes a cross-section of researchers from basic to clinical to population sciences to explore how best to use mouse models to find solutions to common problems. At their initial meeting, in response to the Brain Cancer PRG recommendations for more and improved models, the group delineated priorities for what kinds of models are needed for various translational science questions. One crucial element of their recommendations is incorporation of the latest imaging technologies in as wide a range of applications as possible with the neuro-oncology mouse models. The MMHCC laboratories, in collaboration with the Small Animal Imaging Resource Programs, recently initiated a Mouse Model Imaging Roundtable with the manufacturers of imaging equipment. Their goal is to apply the optimal imaging approaches to the research questions that the model developers and their clinical collaborators choose to pursue. This activity will measurably enhance the effectiveness of translational research using mouse neuro-oncology models.

In summary, brain tumors are a devastating problem in our society, and they remain among the most frightening and refractory of human tumors. Much remains to be learned about the biology of the diverse types of brain tumors that arise in children and about the biology of the high-grade gliomas that predominate in adults. The NCI is seeking to advance understanding of brain tumor biology by supporting research to apply advanced molecular methods to the analysis of human brain tumors and by developing animal models that faithfully replicate the biology of human brain tumors. Translating lessons learned from the laboratory about brain tumors into the clinic requires multidisciplinary and sophisticated resources. NCI continues to foster collaboration among centers of excellence so that studies are completed reasonably quickly and opportunities to accelerate progress are maximized. Maintaining an efficient system to nourish brain tumor research, from the earliest preclinical work to its eventual clinical application, is an NCI priority.

Item

Breast Cancer – The Committee continues to be concerned over the disparity in breast cancer mortality and morbidity among African-American women. The Committee therefore encourages the NCI to report to Congress by **April 1, 2002**, about existing efforts, as well as planned future efforts, to better understand and respond to this disturbing phenomenon. (p. 121)

Action taken or to be taken

The unequal burden of disease in our society is a challenge to science and a moral and ethical dilemma for our Nation. Many American communities and population subgroups experience cancer-related health disparities due to a combination of factors related to genes, individual behaviors, and social and environmental circumstances. The NCI is committed to understanding the causes of cancer health disparities and developing effective interventions to reduce them. To focus energy on maintaining a sound research infrastructure and building capacity to reduce health disparities, NCI's has designated this challenge as among the highest scientific priorities. A major focus of NCI's challenge to reduce cancer health disparities is on breast cancer among

African-American women. Evidence suggests that the causes are complex and multiple approaches will be needed to reduce the burden of this dread disease. Additionally, NCI established new Center to Reduce Cancer Health Disparities, led by Dr. Harold Freeman, a nationally recognized expert in health disparities. The research agenda of the Center includes closing the gap between research discovery and health service delivery.

Breast cancer is the most common cancer among African-American women. Although the incidence rate is lower in African-American women than in white women, the death rate for African-American women is 28% higher than white women. In addition, African-American women are less likely to survive five years after diagnosis. Mortality rates have declined among white women since 1989, but increased for African-American women from 1989, leveling off only in the most recent time period 1995-98. (It is important to note that rates among African-American women younger than 50 declined during that period.) This higher mortality rate may be due to many factors including the types of tumors African-American women develop, the more advanced stage at diagnosis, and the treatment received.

NCI researchers have developed a statistical model to predict the risk of developing breast cancer for a woman with specific risk factors, such as having one or more family members with breast cancer. Because available breast cancer risk projection models were mainly developed using data from white women, NCI scientists plan to utilize recent studies to develop risk models appropriate to minority populations, including African-American women. These models can be used to help counsel African-American women about their risk of breast cancer and also to determine eligibility for entry into clinical trials of preventive medications.

The NCI Surveillance, Epidemiology and End Results (SEER) Program, which began in 1973, recently launched an expansion to include additional high quality registries. In early 2001, awards were made to four additional states (California, Kentucky, Louisiana, and New Jersey) thereby increasing SEER coverage from 14 to 26 percent of the U.S. Population (from 35 million to over 65 million persons). This expansion also substantially increased coverage of African-Americans, Hispanics, American Indians, Asian and Pacific Islanders, persons living in rural areas, and residents of areas with high poverty levels. Expanded coverage to 24 percent of U.S. African-Americans will greatly enhance the capability to track cancer trends in this population.

NCI is committed to research, education, and communication across the cancer control continuum including prevention, early detection and screening, diagnosis, treatment, and survivorship. The Institute currently funds 70 studies, totaling $24 million dollars that address breast cancer among African-American women. Following are examples of ongoing efforts and collaborations with other organizations.

Recent evidence suggests that tumors in African-American women may be different than those of other race-ethnic groups. Compared to white women, African-American women tend to be younger at diagnosis and tend to be diagnosed with estrogen-receptor negative tumors, a form of breast cancer that is associated with a poorer prognosis than estrogen-receptive positive tumors. Research is underway to identify causes of these tumor types in African-American women.

NCI is encouraging grantees with very large studies that identify risk factors that lead to cancer to work cooperatively. Combining studies of the determinants of cancer will achieve greater statistical power to examine subpopulations such as African-Americans. Breast cancer is one of two cancer types to be studied first. Additionally, NCI's Breast and Ovarian Cancer Family Registry is a consortium of multiple institutions dedicated to identifying genetic factors that contribute to breast cancer risk and to examining their interactions with environmental factors. It is estimated that by 2005 the Registry will have enrolled as participants over 700 African-American women with breast cancer, and their families. By including large numbers of African-American breast cancer patients and their close relatives in genetic studies, it will be possible to understand more about he complex causes of breast in this underserved population and identify new opportunities for prevention.

NCI-sponsored Special Populations Networks for Cancer Awareness Research and Training (SPNs) were established at 18 research institutions in 2000 to build relationships with community-based programs, foster cancer awareness activities, and increase minority enrollment in clinical trials, among others. NCI currently supports seven projects through the SPNs to address cancer health disparities in African-American communities across the country. Specific areas are Philadelphia and other African-American communities in the Mid-Atlantic, the Deep South, the New York metropolitan area including Haitian immigrant communities, and Arkansas and the Mississippi Delta regions. SPN efforts in these communities have identified many of the barriers that exist to appropriate screening, follow-up and treatment. As a result, health education curricula are being developed that are sensitive to cultural, linguistic, and education barriers to screening and follow-up for African-American women.

African-American women are more often diagnosed with cancer at an advanced stage, which is more difficult to treat and is associated with a worse prognosis. They also have historically lower and less-regular mammography screening rates, and longer delays after an abnormal mammogram.

Mammography screening is vital to early detection of tumors and rapid diagnosis and treatment. NCI currently supports over $1.0 million in research grants to identify and mitigate barriers to breast cancer screening by African-American women. Collaborations with the Centers for Disease Control and Prevention (CDC) are underway to support new intervention research on barriers to screening for women who under use or never use breast and cervical screening and on sociocultural determinants in planning, implementing, and evaluating these interventions.

Cancers among African-American women are more frequently diagnosed after the cancer has metastasized and spread to other sites. These statistics and research findings showing similar disparities prompted NCI's Center to Reduce Cancer Health Disparities (CRCHD), under the leadership of Dr. Harold Freeman, to support two major initiatives highlighted below. These initiatives are designed to examine growing evidence that socioeconomic, cultural, health care provider, institutional, and environmental factors contribute substantially to cancer-related health disparities:

1. NCI has assembled a cadre of experts from various medical and social science disciplines to examine why patients with equivalent cancer diagnoses and similar financial resources and access to care have differing levels of cancer care by race and ethnicity. Using a

"think tank" model they are discussing whether, as the literature suggests, an effect of race/ethnicity/culture on cancer treatment and/or outcome exists that is distinct from access, socioeconomic status, or other factors. The short-term goal of this initiative is to determine what is known that can explain these disparities in cancer care, disseminate the evidence, and identify areas where research may be needed.

2. The Center also is exploring alternative frameworks to conduct an examination of the cost of cancer care for the uninsured. Issues to be examined include the cost to the Nation to provide health care coverage for the uninsured when they are presented with a diagnosis of cancer. Other issues include a cost comparison to the current system of care where the uninsured tend to be diagnosed with cancer in the later stages of disease and receive late stage treatment regimens that are very costly, and have low survival rates.

African-American women respond similarly to other groups in terms of response treatment in clinical trials of therapies. That is, when stage of disease and treatment are comparable, outcomes for African-Americans and Caucasians do not differ markedly. However, studies outside of clinical trials or very accessible health care settings have found disparities in health care including less frequent receipt of recommended care by African-American women.

There is research evidence that surgical treatment of women with early-stage breast cancer varies greatly, depending on where they live, their income and education, and characteristics of their surgeon and the medical facility used. NCI, along with the Agency for Healthcare Research and Quality, as well as several other federal organizations, are providing funding support for a December 2001 conference on "Using Research to Inform Patients of Breast Cancer Surgery Options." The conference will bring together experts representing researchers, health professionals and providers, and patient advocates, to develop strategies to increase the likelihood that all women (regardless of their income, age, race, ethnicity, where they live, and where they receive medical care) with early-stage breast cancer will be accurately informed about their treatment options. Recommendations from the conference will be used to develop educational materials for patients, health professionals, and advocates. Additionally, NCI developed a new series of cancer patient education materials about clinical trials that was created specifically for African-American groups and intended to increase the numbers of African-Americans who participate in clinical trials.

African-American women may experience greater morbidity from breast cancer because of the presence of multiple medical and psychosocial conditions, and potentially less access to cancer care and supportive services. NCI funds various studies that are examining different aspects of this issue. In the past year alone, NCI funded three pilot projects through the Comprehensive Cancer Centers focusing specifically on African-American breast cancer survivors. These projects will examine a) use of community social support services; b) follow-up care and surveillance activities; and c) a culturally relevant peer-counseling program to improve sexual function and decrease infertility-related distress among African-American breast cancer survivors. Other research studies are investigating issues such as the interrelationship between cognition, emotion, biological processes, and physical health; the impact on family of survivorship from cancer; differences in long-term quality of life and predictors for cancer recurrence; the prevalence of long-term effects of cancer and the impact on quality of life; and the effect of screening behaviors on length and quality of survival.

Disparities in morbidity and mortality from breast cancer among African American women are a complex, multi-faceted phenomenon that does not lend itself to simple solutions. These disparities involve the interplay of many factors including biological, social, and economic factors at a minimum. Targeted, focused research on these various aspects of the problem is necessary, yet an interdisciplinary, multilevel approach to the problem is also important. The NCI's proposed Centers for Population Health and Cancer will provide a structure and an impetus for generating such research on the question of African-American breast cancer and other cancer health disparities.

Research into the causes of breast cancer, detection, treatment, and survivorship has led to significant insights about why these disparities are occurring. In turn, this new understanding is leading to research on entirely new approaches in cancer prevention and control to reduce these significant disparities. NCI and its partners are poised and determined to understand the effectiveness, benefits and risks of interventions to prevent and control breast cancer among African-Americans, and to assure dissemination of interventions specifically aimed at reducing health disparities.

Item

[Tumor Cells] -- The Committee is aware of the importance of restoring sensitivity of tumor cells to standard chemotherapy drugs by reversing the effects of low oxygen stress on the cells. Cancer researchers have developed methods of achieving this important scientific tool, and the Committee encourages the NCI to consider this important research. (p. 121)

Action taken or to be taken

The NCI is actively pursuing leads involving tissue/cellular hypoxia and its effects on chemoresistance. Currently, the NCI is the lead developer of the 2-nitroimidazole derivative, EF-5, which is being evaluated in Phase I trials where EF-5 is being combined with standard chemotherapy and radiation therapy approaches. If the Phase I work is successful, the NCI will consider moving this agent into Phase II trials in tumor types like breast cancer where hypoxia may play a role in chemoresistance. Additionally, the NCI is aware of new reports indicating a potential role for nitrous oxide mimetic drugs to counteract cellular hypoxia. This lead is being pursued with appropriate investigators.

Item

Breast Implants – The Committee encourages the NCI to continue to collect and analyze data from the women in its three recent studies of the health risks of breast implants, to determine whether there is a link between breast implants and breast cancer, other cancers, or mortality from all causes. (p. 121)

Action taken or to be taken

NCI intramural scientists have conducted a retrospective cohort study, the Women's Health Study, to assess the long term health effects of silicone breast implants. Analyses of cancer risk in this study have been completed, showing no alteration in the risk for most cancers, including

breast cancer, which has been of concern given evidence that implants interfere with the mammographic visualization of breast lesions. Patients in the study did experience an elevation in the risk of lung and brain cancers, although the reasons for the excesses were unclear. Results from published analyses of mortality showed that women with implants were not at increased risk for most causes of death compared to controls, except for the cancers mentioned above. Currently underway are analyses of the risk of connective tissue diseases related to breast implants. The characteristics of the 13,500 participants and 4,000 comparison patients in the study have been described in a publication.

A number of studies have evaluated the relationship between breast implants and subsequent breast cancer risk. Most have shown that the risk of developing breast cancer is somewhat reduced among women with implants compared to women without implants. However, these studies generally did not have detailed information on patient characteristics that could affect the development of breast cancer, and had follow-up times of less than 10 years. NCI researchers found a slight decrease in breast cancer risk during the initial 10-year period. However, this decrease was not seen with increasing follow-up time. The NCI researchers also found a shift toward somewhat later detection of breast cancers among implant patients compared to the controls. However, there was no significant difference in breast cancer mortality between implant and comparison patients. Further surveillance of breast cancer death rates among implant patients is recommended.

When the cancer rates among the implant patients were compared to other plastic surgery patients, the rates for nearly every cancer, including mouth, stomach, large intestine, breast, cervix, uterus, ovary, bladder, thyroid, connective tissue, and immune system were not increased among implant patients. Prior anecdotal reports suggested that implant patients may have increased risks for tumors that develop from connective tissue, such as soft tissue sarcomas, or for cancers of the immune system, such as lymphomas and leukemia. However, the NCI researchers did not find an increased risk of sarcomas among implant patients, nor did Hodgkin's or non-Hodgkin's lymphomas develop at higher rates. Further, no increased risks were seen for multiple myeloma, a cancer site that has been of concern given its development in laboratory animals exposed to silicone. The only cancers that were greater in the implant group compared to the plastic surgery control group were respiratory and brain cancers. However, it is possible that the higher risks observed for respiratory and brain cancers are not related to exposure to silicone, but are due to either chance findings or to factors common to women who choose to have implants.

The NCI study is one of the few to look at all causes of mortality of breast implant patients. Previous reports have focused on mortality from breast cancer and found, as in the NCI report, no increased risk in breast cancer mortality for implant patients compared to the general population.

The NCI researchers found that nearly every cause of death – including all cancers, circulatory and digestive system disease, endocrine, nutritional, metabolic and immune disease, and cirrhosis of the liver- was decreased among implant patients. The lower mortality rates of the implant population support previous findings that people who undergo elective surgery are generally healthier than their peers in the general population.

The lower rates are due primarily to fewer deaths from cancers and diseases of the circulatory system, the most common causes of death in the general population. The exceptions to the lower rates were deaths from brain cancer, suicide, pneumonia and emphysema. Breast implant patients were two to three times more likely to die from brain cancer, and nearly twice as likely to die from suicide, pneumonia, and emphysema, compared to the general population. The researchers also found, after 15 or more years of follow-up, an increased risk of respiratory tract cancer among implant patients.

The NCI researchers previously showed that other plastic surgery patients may be a more appropriate comparison group than women in the general population for studies of the health effects of breast implants because of certain similarities between the two groups of patients. These include the number of pregnancies, previous gynecologic operations, and operations for benign breast disease, levels of alcohol consumption, and rates of cigarette smoking.

Although both plastic surgery groups have lower mortality rates than the general population, in the NCI study women with breast implants had slightly higher overall mortality rates than other plastic surgery patients. Specifically, the researchers found that implant patients were three times more likely to die from respiratory tract cancer, two to three times more likely to die from brain cancer, and four to five times more likely to die from suicide. The higher suicide rates of the implant patients correlate with characteristics described among implant patients in previous reports – marital difficulties, depression, emotional disorders, and low self-esteem. NCI researchers plan to follow the cohort for updated mortality status, and to continue to evaluate the observed excess risks of lung and brain cancers, and of suicide. Analyses regarding silicone breast implants and connective tissue disorders are under way.

Item

Cancer and Minorities –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. 122)

Action taken or to be taken

Since 1973, cancer incidence, survival and mortality data have been collected and reported on Native Hawaiians. The state of Hawaii and significant areas in California (Greater Bay area of San Francisco and Los Angeles County) are an integral part of the NCI Surveillance, Epidemiology, and End Results (SEER) Program. The SEER Program is in the process of developing an updated monograph on racial and ethnic cancer rates and trends, with specific information for Native Hawaiians as well as other racial/ethnic groups. Publication is scheduled for Spring 2003 as population data for 2000 must be available by states in order to calculate recent cancer rates.

NCI continues to provide additional funds for special surveillance and cancer control studies in populations covered by the SEER registries. Collaborative studies that include Native Hawaiians have focused on quality of life outcomes in long term survivors of cervical cancer, cancer risk and prognostic factors, and alternative medicine treatment. As an outgrowth of an NCI funded training program for researchers in cancer control, five pilot research projects have been supported that are conducted by Native Hawaiians within their community. These include:

- Hawaii: Infant Leukemia among High Birth Weight Infants
- Puna, Hawaii: Native Hawaiian Women and Breast Cancer
- Maui, Hawaii: Barriers to breast and cervical cancer screening among Native Hawaiians
- Honolulu, Hawaii: Spirituality among Native Hawaiian Cancer Survivors
- Honolulu, Hawaii: Knowledge, Attitudes and Practices Regarding Breast Cancer among Native Hawaiians.

In FY 2001, three new projects were conducted in Native Hawaiian communities:

- Honolulu, HI (Papa Ola Lokahi): Spirituality and Acculturation in Native Hawaiian Cancer Survivors: Implications for Intervention. Findings will be presented to research participants and the Native Hawaiian Community, as well as to other agencies and organizations. The research is being conducted by a Native Hawaiian investigator as part of a her doctoral program.
- Honolulu, HI (University of Hawaii): Validating A Measure of Religiousness/Spirituality for Native Hawaiians. This project will attempt to validate a measure of religion and spirituality appropriate for Native Hawaiian women cancer survivors and will include about 140 study participants. Findings will be disseminated and discussed within the Native Hawaiian community as well as prepared and submitted to a journal for publication.
- Honolulu, HI (Papa Ola Lokahi): Identifying Motivators and Barriers to Breast and Cervical Cancer Screening among Kanaka Maoli Women living on Maui. Kanaka Maoli women (Native Hawaiian women) have the highest breast and cervical mortality rates in the state of Hawaii. Using results from the Kokua program on Maui which serves close to 500 women, the research will address the problem of late diagnosis, by examining factors associated with high screening non-adherence rates among the group of 80 women over age 40.

With respect to NCI's overall research investments, in fiscal year 2001, the Institute funded 19 extramural research and training grants totaling over $22 million in involving Native Hawaiians, with over $8 million of these funds to organizations within the state of Hawaii. This represents a 19 percent increase in funds from FY 2000 to FY 2001. In FY 2000, NCI funded the Special Populations Networks for Cancer Awareness and Training to invest resources in building community-based infrastructure to support participatory research and education with populations that bear the greatest burden of cancer. One of the Special Populations Networks focuses on Native Hawaiians.

In FY 2001, the 'Imi Hale - Native Hawaiian Cancer Awareness Research and Training Network is in its second year of a five year cooperative agreement project with $2.5 million of NCI support. This project is housed within Papa Ola Lokahi, a consortium of Native Hawaiian non-

profit organizations and public agencies with the single purpose of improving the health and wellness of Native Hawaiians. ‘Imi Hale provides the cancer awareness and research infrastructure for Native Hawaiians in the state through memoranda of agreement with community organizations and key institutions including the Cancer Research Center of Hawaii, the Cancer Information Service (Hawaii), Kamehameha Schools, and the Native Hawaiian Center of Excellence (University of Hawaii School of Medicine). This year, two pilot projects were approved for additional funding of $50,000 each. These projects include a study of breast cancer in Native Hawaiian women and the training of Native Hawaiian high school students to develop cancer drugs for testing. Other achievements include the development of a Native Hawaiian Institutional Review Board, with representation from all the islands, to approve research projects and involve community-based leaders in the research process. In addition, the report on *Tobacco Use, Prevention and Control: Implications for Native Hawaiian Communities* has been completed, representing the first published document to address tobacco use in Native Hawaiian communities.

In the area of cancer awareness, `Imi Hale works with Community Outreach Staff from the Native Hawaiian Health Care Systems to disseminate current and timely information and to implement the activities identified in the strategic plans developed by each island community. Each of the islands had their own cancer awareness activities on the themes of smoking cessation, timely cancer screening, diet/nutrition and exercise. `Imi Hale also developed a series of four culturally competent breast cancer education “talk story” booklets, entitled *Discovering We Had Breast Cancer, Breast Health Care, Post-Diagnosis: Now What?* and *The Importance of ‘Ohana (Family) in Survivorship*.

Item

Cancer Centers – The Committee recognizes the high quality of care provided by NCI-designated Cancer Centers, but notes that many cancer patients must travel great distances to receive care from these centers. In addition, many other smaller institutions provide excellent patient care, perform high-caliber basic research, address unique cancer prevention and treatment issues, and lend great expertise to cancer treatment and control. The Committee encourages the NCI to further expand their Cancer Centers Program and give full consideration to applicants that care for a large number of underserved patients from rural and economically distressed areas. (p. 122)

Action taken or to be taken

The Cancer Centers Program of the NCI supports major academic and research institutions throughout the United States to sustain broad based, coordinated, interdisciplinary programs in cancer research. These institutions are characterized by scientific excellence and capability to integrate a diversity of research approaches to focus on the problem of cancer. The NCI and its Cancer Centers Program are dedicated to the advancement of cancer research to ultimately impact on the reduction of cancer incidence, morbidity, and mortality.

Requests from eligible institutions for cancer center support are subjected to a competitive peer review process that evaluates and ranks applications according to scientific merit. Successful

applicants are awarded a P30 Cancer Center Support Grant (CCSG) to fund the scientific infrastructure of the cancer center, including such elements as scientific leadership and administration; research resources that give ready access to the state-of-the art technologies; and flexible funds that help the center pursue its planned objectives and take immediate advantage of new research opportunities.

Each institution receiving a CCSG award is recognized as an NCI-designated Cancer Center. There are three types of cancer centers based on the degree of specialization of their research activities. The generic cancer centers have narrow research agenda that may focus, for example, on basic sciences; the clinical cancer centers usually integrate strong basic science with strong clinical science; and the comprehensive cancer centers integrate strong basic, clinical, and prevention, control, and population sciences. Although the CCSG is mainly awarded to support research infrastructure, all clinical and comprehensive cancer centers also provide clinical care and service for cancer patients. In addition, comprehensive cancer centers have extensive ancillary cancer-related activities such as outreach, education and information dissemination, as do some clinical centers to a more limited extent. Through all of these activities combined, clinical and comprehensive cancer centers play an important role in their communities and regions and serve to influence standards of cancer prevention and treatment. Importantly, all NCI-designated Cancer Centers, which also include generic cancer centers, make contributions to advances in cancer research that are key to understanding, preventing, and treating this disease.

The NCI agrees that the Cancer Centers program should be expanded to underserved areas of the nation. Over the last ten years working through traditional application and review processes, this objective has been met. This is one reason why the planning grant for developing new cancer centers was extended from a 3-year to a 5-year grant period; it allows smaller institutions in underserved areas of the nation more time to develop a high quality research enterprise that effectively links research to patients and populations. With this change in planning grants, the NCI is actively engaged with institutions in the states of South Carolina, Oklahoma, Kentucky, Louisiana, Georgia, and New Mexico. None of these states currently has an NCI-designated cancer center, but all have the potential to reach that goal within a 3 to 5 year time line . In addition, dialogues continue with institutions in the states of Arkansas and Missouri. With changes in strategy that began several years ago, the NCI believes that the Cancer Centers program will indeed be expanded.

Item

Chronic Lymphocytic Leukemia (CLL) – The Committee urges the NCI to increase research on CLL, its underlying cause, and improved therapies. The Committee is pleased to learn that the NCI awarded a program project grant last year to establish and lead a multidisciplinary national research consortium to study CLL at both the cellular and clinical levels. The Committee strongly encourages the NCI to give full and fair consideration to expanding the scope of research activities funded through the CLL Research Consortium and the participating partners involved. (p. 122)

Action taken or to be taken

Please refer to pages NCI-51 through NCI-53 of this document for NCI's response to this significant item regarding Chronic lymphocytic leukemia (CLL).

Item

Complementary and Alternative Cancer Therapies – The Committee expects NCI to expand its work and its collaborative efforts with the National Center for Complementary and Alternative Medicine to support 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 a rigorous scientific review of them. (p. 122-123)

Action taken or to be taken

The NCI and the NCCAM continue to collaborate on various complementary and alternative medicine (CAM) initiatives.

One such research collaboration includes the Innovative Cancer Complementary and Alternative Medicine Initiative in NCI-designated Cancer Centers. The NCI and NCCAM have each committed 1 million dollars per year over the next three years to support high-quality programs at six (6) NCI-designated Cancer Centers. The development of this program included the solicitation of applications and performance of a competitive review of pilot projects (basic and clinical) in any of a variety of CAM approaches. The research will be performed at comprehensive and clinical P30 cancer centers with the participation of CAM practitioners in the research process. The long-term goal of the program is to increase the number of successful R01 CAM cancer applications submitted to and funded by the NCI and NCCAM.

NCI and NCCAM continue to jointly support the prospective trial at Columbia Presbyterian Medical Center examining the effect of the "Gonzalez regimen" (a nutritional program with oral pancreatic enzymes and a "detoxification" regimen) on survival rate and quality of life among patients with Stage II, III, or IV pancreatic cancer.

In addition, a study of the use of oral shark cartilage in combination with conventional chemotherapy and radiation in patients with advanced, non-small cell lung cancer began accruing patients in April 2000. The study is being performed via the MD Anderson Cancer Center Community Clinical Oncology Program. A second trial of a different formulation of oral shark cartilage (powdered) also has begun. This trial is for patients with advanced breast or colorectal cancer and is being performed by the North Central Cancer Treatment Group with primary oversight by the research base at the Mayo Clinic.

In the arena of Cancer CAM information, NCI and NCCAM collaborated to co-sponsor with the Center for Mind-Body Medicine, the Comprehensive Cancer Care IV Conference in October 2001. The NCI presented three concurrent sessions at this conference discussing how to perform a best case series; opportunities for funding of CAM cancer research; and symptom management.

In addition to the collaborative research efforts with NCCAM, the NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) Research Development and Support Program is facilitating other research programs and workshops to encourage high quality CAM research and the bridging of practice and research communities to form research partnerships.

OCCAM solicited and reviewed applications from the NCI's Cooperative Groups and Community Clinical Oncology Programs for supplementary funds to support CAM-related clinical trials with the primary goals of this initiative being to support trials of approaches with greatest likelihood of providing benefit to cancer patients.

OCCAM will be developing a series of expert panels to explore the major research methodology challenges in performing high-quality CAM research. The goals of these groups will be to review the state of the science in a particular area and generate documents that will be used to educate grant applicants and reviewers. Examples of these planned topics for these panels include CAM cancer symptom management and botanicals.

OCCAM will be sponsoring a two-day Technical Assistance (TA) Workshop for investigators interested in cancer complementary and alternative medicine research to be held in the Washington D.C. Area. This two-day workshop, to be held in early 2002, is intended to assist researchers in the development of applications for cancer CAM research funding from NIH.

OCCAM is devoted to bringing the latest cancer CAM research data to the NIH community to encourage intramural CAM cancer research and collaboration and to increase awareness among the extramural program staff. A seminar series has been initiated with funding from the OCCAM. In January 2002, the first panel presentation focusing on state-of-the science research data on acupuncture will be held.

OCCAM has made the Practice Assessment Program (PAP) a high priority for the upcoming year. The two components of the PAP are the Best Case Series program and the Prospective Outcomes, Monitoring, and Evaluation (POMES) program.

The Best Case Series program affords opportunities for CAM practitioners to submit their best clinical case studies using alternative interventions. Medical records, diagnostic imaging, operative, pathology reports are submitted to the OCCAM which evaluates and summaries each case study, arranges the review of the original radiology and pathology slides, and plans for the presentation of data before the Cancer Advisory Panel for CAM (CAPCAM). There have been four completed case reviews, and two practitioners have presented their case studies before CAPCAM. NCI is promoting the Best Case Series program for CAM practitioners via direct mailings, congress sessions, and notices in conventional and CAM publications.

The OCCAM website (http://cancer.gov/cam) continues to serve as a communication link to the general public, research and practice communities. The site contains descriptions of current and planned NCI CAM initiatives; projects a visible research agenda; provides information about funding opportunities, CAM fact sheets, and upcoming conferences; links to other pertinent websites; and explains the NCI's processes for handling CAM issues (e.g. the Best Case Series Program).

The NCI, through the OCCAM and the Office of Cancer Communication, and with the assistance of the NCCAM, is developing summaries of the literature about various CAM modalities. These summaries are available on the CancerNet website (http://cancernet.nci.nih.gov) or from the Cancer Information Service (1-800-4CANCER). Seven such summaries have been developed and new summaries will be completed and fully reviewed quarterly. In addition, fact sheets derived from these CAM literature summaries are being developed. The CAM fact sheets provide the same information, but are written for the lay public and designed in a more accessible question and answer format.

Several CAM-related projects are being implemented via the NCI's Center for Cancer Research in areas such as diet, vitamin and mineral research. In addition, in the Division of Cancer Epidemiology and Genetics several CAM-related nutritional studies are underway.

NCI continues to support high quality research applications in CAM areas such as stress management affects on survival; effects of soy products on breast cancer risk; and various studies on vitamins/minerals and other natural products. In addition, numerous CAM studies have been implemented via the NCI Community Clinical Oncology (CCOP) program.

The largest of these studies is the SELECT Trial (Selenium and Vitamin E Cancer Prevention Trial) which began in July 2001. This study will recruit 32,400 men, 55 years old and older, to determine if selenium and Vitamin E can protect against prostate cancer. More than 400 sites in the US, Puerto Rico, and Canada are recruiting participants for SELECT, which will take 5 years to complete.

OCCAM will be implementing a multifaceted exploration of the issues involved in expanding high-quality CAM cancer research. This project includes data gathering about CAM cancer research projects submitted to the NCI and other government and non-government funding organizations with scientific peer review processes. In addition, surveying will include assessing CAM practitioners and cancer researchers to determine their participation in CAM research and interest in partnership.

OCCAM will be hosting a focus group where CAM practitioners and cancer researchers will offer ideas about how the two communities may partner in CAM research initiatives. The one-day meeting will be held in the Washington D.C. Area in Spring 2002. The information obtained will offer insight on how to heighten awareness of CAM research initiatives, potential partnerships and funding opportunities.

Numerous concepts for clinical trials on CAM topics are under review. Fxamples of these concepts include: mindfulness relaxation and chemotherapy; lycopene in the prevention of prostate cancer; Coenzyme Q10 in the relief of fatigue; treatment of cachexia using nutritional supplements; and use of kava for patients with recurrent colon cancer.

The NCI intends to work with the NCCAM and the CAM and conventional research and practitioner communities to identify important and promising CAM approaches to cancer management and to facilitate their scientific evaluation. We will increase access of CAM practices to the processes of scientific review and evaluation at the NCI and NIH. This will be

accomplished by the OCCAM providing assistance to direct the referral of these individuals to the appropriate groups within the NIH.

Item

Diethylstilbestrol (DES) – . . . . the Committee urges NCI to continue its agreement with CDC to implement a national education program for consumers and health professionals. 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. 123)

Action taken or to be taken

In partnership with NCI, CDC is leading the development and implementation of a national campaign to inform both consumers and health professionals about the potential health effects associated with Diethylstilbestrol (DES) exposure. Originally prescribed for pregnant women between 1938 and 1971 to prevent miscarriages, DES, a synthetic estrogen, is now linked to increased risks of cancer, genital abnormalities, and/or compromised fertility. An estimated 5 to 10 million individuals are at risk; this includes women who took the drug while pregnant, as well as their children. Since the initial campaign planning meeting held at NIH in 1999 called DES Research Update (Proceedings available online, http://planning.cancer.gov/whealth/DES/index.html), there have been two main phases of the campaign. The Program Development phase focused on two main areas, one, research and planning and two, message and materials development. The second phase is Campaign Implementation, a key element of which has been the development of partnerships to help support and carry out the campaign. An evaluation of the campaign is also planned for the future.

In the Program Development phase, the campaign planners needed to assess current knowledge, attitudes, and receptiveness toward information about DES exposure among target groups. Over the last two years, formative research was conducted in the form of focus groups and interviews with selected target audiences of consumers and health professionals. A key finding from the 30 focus groups and 29 interviews conducted was that the strategy to reach health professionals should not be limited to physicians, but should also include affiliate health professionals, such as physician assistants and nurse practitioners, as they were more receptive to learning more about the issue. Regarding consumers, the researchers found that within the known-exposed populations, daughters born from mothers who took DES were more knowledgeable about DES than compared with sons or even with the mothers themselves. The research also showed that all of these groups were interested in learning more about ongoing DES research, including the potential effects on grandchildren. Following the formative research, the campaign planners used the results to draft a Strategic Communication Plan in December of 2000. To guide campaign efforts, this plan set forth campaign goals and objectives, profiled potential target audiences, and outlined message and dissemination strategies.

Based on developed and tested message concepts, the campaign planners developed a comprehensive set of consumer materials, including fact sheets, guides to understanding

scientific research, summaries of recent studies, and tips for talking with health professionals. Also developed was a "DES Checkup," which lists questions to help determine the likelihood of a person's DES exposure, as well as next steps to take. All consumer materials are being pre-tested and will be available in December 2001.

To develop professional education and training materials for the campaign, the CDC partnered with the Office of Women's Health and their five Centers of Excellence (CoEs) in September of 2000. The CoEs, respectively, are developing DES courses for self-paced study or CEU/CME credit, a comprehensive web site housing both consumer and health professional information on DES, grand round presentations, case studies for medical student curriculum, and journal articles for specific medical journals. The materials are being reviewed by a panel of DES experts and are being pre-tested with health professionals.

In planning and in the development and testing of materials, the campaign planners have partnered successfully with a Working Group comprised of members from consumer advocacy organizations, women's health organizations, government agencies, and medical professional associations. The campaign planners will continue to work closely with the Working Group in the implementation of the campaign.

In preparation for the second phase, Campaign Implementation, CDC completed an audit of about 50 organizations to identify their target audiences and/or members, their missions, and the types of information that they provide. Once DES materials are finalized and available, CDC will approach appropriate organizations to encourage them to include information about DES and link to the DES web site.

Full implementation is scheduled for spring of 2002 and entails the development of a plan for the dissemination of campaign materials, the actual dissemination of campaign materials, integration of DES messages into related health education materials, and initiation and maintenance of electronic channels of DES information. Plans call for DES messages to be embedded in on-going institutional materials and programs. Once initial dissemination occurs, DES education is expected to become part of extant medical training programs and consumer outreach efforts. As the campaign progresses, message penetration and outcomes will be monitored and corrective adjustments made.

In the future, a Campaign Evaluation is also planned. This effort will include gathering baseline data on public and provider DES awareness, knowledge, and behaviors and assessing campaign impact immediately following the intervention. To measure long term campaign impact, two follow-up assessments are planned at one year intervals following the initial post-intervention evaluation. The evaluation will also include individual assessment of specific campaign tactics to identify the influence of specific interventions.

Several lines of evidence suggest that hormonal exposures early in life, including *in utero*, may influence risk of breast and other hormonally-related tumors in adults. To assess this hypothesis, NCI researchers have worked closely with five collaborating centers to reassemble and combine the U.S.-based cohorts of DES-exposed daughters, sons, and mothers that were studied in the 1970s and 1980s.

Compared with unexposed women, NCI researchers found that exposed mothers had a 10% overall excess risk of incident cancers of all sites combined. This excess was essentially all due to a 30% increase in breast cancer risk that appeared within the first 10 years following exposure, similar to that observed for oral contraceptive and menopausal hormone use. However, unlike these other hormonal effects, the DES effect persists for at least 40 years following cessation of the exposure. There were no significant differences between exposed and unexposed mothers for any other cancer sites.

Overall, the frequency of all cancers combined among women exposed *in utero* to DES was similar to those not exposed and to expected rates based on general population experience. However, cases of vaginal or cervical clear-cell adenocarcinoma among DES-exposed women were 40 times greater than expected. I*n utero* DES exposure was also associated with an excess risk of squamous dysplasia of the cervix and vagina, along with evidence to suggest that the relative risk was greater the earlier in the pregnancy that the fetus was exposed.

The small population of men exposed *in utero* who were available for study made it difficult to assess cancer risks among these men. Overall, no excess risk was observed for all sites combined, while the relative risk for testicular cancer was twice as great as that in the general population and three times that of unexposed sons.

The NCI DES Follow-Up Study will continue to focus on the long-term health effects of DES exposure. The study, which began in 1992, has sent questionnaires to more than 15,000 women and men in 1994 and 1997. The 1997 questionnaire, which was distributed to over 6,500 daughters and 3,600 sons who were exposed to DES *in utero* as well as to unexposed individuals, had a greater than 90% response rate. The third questionnaire, which was mailed to study participants in the summer of 2001, was similar in length and in the types of questions that were asked. Standardization of the questionnaire over time allows NCI researchers to compare any changes in the health habits and experiences of the respondents over time.

In addition, in response to concerns about possible multi-generational effects of DES exposure in humans, a new initiative is underway to systematically follow the granddaughters of women who took DES during pregnancy. The Third Generation Study, which was launched in August 2000, is enrolling adult daughters of women who participated in the DES daughters' study. The study will compare the two groups of third-generation women, those whose mothers were exposed to DES and those whose mothers were not exposed. It is anticipated that 700-800 young women from all five U.S. Research centers will enroll. Study participants will be asked to complete a mailed questionnaire describing their medical, gynecological, and reproductive histories. Women who report certain breast or gynecological diagnoses will be asked for permission to obtain their medical records to confirm the diagnoses.

Item

Gynecologic Cancer – . . . .The Committee strongly urges NCI to expedite current research on screening methods to detect, diagnose, and identify staging of ovarian cancer. The Committee is pleased that NCI has fully funded four ovarian cancer SPOREs, and it encourages the Institute to consider issuing a new request for applications for additional ovarian cancer SPOREs. The

Committee also believes that identification of a cost-effective screening strategy could result in earlier diagnosis for women and higher cure rates. NCI is strongly urged to accelerate research in this area. (p. 123)

Action taken or to be taken

Please refer to pages NCI-69 through NCI-73 of this document for NCI's response to this significant item regarding Gynecologic cancer.

Item

Imaging Systems Technologies – The Committee is encouraged by progress made by NCI following its August 1999 conference on biomedical imaging, and it urges NCI to continue to take a leadership role with the Health Care Financing Administration and the Food and Drug Administration to avoid duplicative reviews of new imaging technologies that 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). The Committee continues to support NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee continues to encourage the large-scale testing of women for breast cancer and of men for prostate cancer to demonstrate and quantify the increased diagnostic and staging capabilities of PET relative to conventional diagnostic and staging technologies, including mammography. (p. 123)

Action taken or to be taken

NCI funds approximately 39 investigator-initiated grants related to PET and microPET imaging technologies. There is a balance of topics ranging from development of new detectors and system instrumentation to investigation of new agents for molecular imaging. Twelve instrumentation projects include development of high-resolution detectors, hybrid micro CT/PET system for in-vivo screening in mice, and methodology for clinical imaging with a PET/CT scanner. Eight projects focus on investigation of new agents for molecular imaging of cancer. Three projects focus on statistical methods for quantitative PET and PET imaging resources for mouse cancer models. Sixteen additional projects span a wide range of topics including pre-clinical studies of gene expression and clinical studies of musculoskeletal, esophageal and colon cancers.

In addition, NCI has awarded 3 P50 center grants to support "In vivo Cellular and Molecular Imaging Centers (ICMICs)" and 16 P20 Pre-ICMIC planning grants. All of the P50 centers, and the majority of the P20 pre-centers have investigations in applications of PET technology. Furthermore, NCI has awarded 10 grants to fund Small Animal Imaging Resource Programs (SAIRP), the majority of which make use of microPET technologies.

Specifically with regard to clinical PET studies in prostate and breast cancer, the NCI is funding three major projects via the In-vivo Cellular and Molecular Imaging Centers, which will increase our knowledge of the microenvironment and the metastatic potential of prostate cancer and the

effects of therapy. These are pre-clinical studies in animal models of prostate cancer as well as translational research studies in humans. Several other investigators have recently received funding to develop new PET ligands that target specific androgen receptor systems known to be important in prostate cancer biology and metastatic spread. These androgen-based systems for detection may lead to targeted radiotherapy ligands for treatment.

Several PET studies are in progress for the evaluation, staging and monitoring of therapy using PET for woman with breast cancer. This includes a large multi-center study based at Johns Hopkins using FDG to assess both the diagnostic utility and staging capabilities of PET. There are also several smaller clinical studies recently funded throughout the country (including Washington University and University of Washington) using FDG as well as newer PET compounds to measure proliferative activity of breast tumors and other important biological variables.

In a large clinical trial from the University of Pennsylvania will incorporate dedicated breast PET into the standard diagnostic regimen for women with breast cancer. In addition to quantifying the relative diagnostic performance of these modalities, individual features extracted by human observers will be studied for reliability and predictive value.

Biomedical opportunities and scientific advances drive technology development in cancer imaging, but NCI recognizes that the regulatory environment in which this development takes place is important. To facilitate the transition of emerging cancer imaging technologies into medical practice, NCI has created venues for interagency dialogue with technology developers through national public meetings, as well as through confidential settings. Since September, 1999, NCI has co-sponsored with industry an annual national conference on biomedical imaging in oncology that focuses on the research, regulatory, and reimbursement pathways of technology development. Topics have included the preclinical and clinical issues in molecular imaging as well as focused attention on the use of anatomic imaging. The conference engages about 200 to 250 participants, and the next one is scheduled for January 30-February 1st, 2002 in Arlington, VA.

In addition, the NCI created and coordinates a sounding board of Federal agency staff that advises investigators and manufacturers seeking to bring new imaging technologies to the marketplace. This group, the Interagency Council on Biomedical Imaging in Oncology, consists of staff from the NCI, the FDA, and the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration). Council members provide product development advice in a private, confidential setting to technology developers from academia and industry. The Interagency Council, begun in June, 2000, meets 3 times per year, and will hold its next meeting on November 19th, 2001. The general topics have included optical, MRI, CT, US, and PET modalities in a variety of cancers and clinical settings. The stage of development has ranged from early to mature technology. The initial feedback from the technology developers is positive.

This interagency venue has also facilitated discussions on areas of mutual interest for the agencies. For example, NCI, CMS, and FDA held a joint workshop in July, 2001 to consider decision-making frameworks for the evaluation of diagnostic tests in imaging.

Item

Melanoma – The Committee is aware of numerous epidemiologic accounts and personal stories of melanoma. The Committee believes that public knowledge of overexposure to sunlight and its connection with melanoma may be lacking. The Committee urges the NCI to continue seeking new therapies for melanoma as well as educate the public through campaigns that encourage appropriate protection from sunlight. (p. 124)

Action taken or to be taken

Melanoma is the most rapidly increasing cancer in the United States and is virtually lethal once it has spread beyond the initial site. Recent metastatic melanoma studies provide some of the first examples of the successful application of specific immunotherapy for human cancer based on an understanding of the molecular basis of the immune response against the disease.

Substantial progress is being made in the development of immunotherapies for the treatment of patients with metastatic melanoma. The genes encoding multiple cancer antigens have been identified and these have been used to develop vaccines that are capable of raising anti-tumor immune responses in patients with cancer. In pilot clinical trials, improved regression of melanoma metastases was obtained by treating patients with these vaccines plus the administration of interleukin-2. In particular, many patients vaccinated with gp100 melanoma antigen found on the outside of melanoma cells, have produced immune cells that attack their cancer. In a preliminary trial, one-third of all metastatic melanoma patients experienced tumor regression when this vaccine was administered along with the immune stimulating cytokine, Interleukin-2 (IL-2). (IL-2 is produced by certain white blood cells and can help boost immune response.)

Patients are experiencing substantial tumor regression in pilot studies of vaccination with a number of other antigens characteristic of melanoma cells, without the help of IL-2 or other immune boosting cytokines.

Efforts to improve these cancer vaccines and cell transfer immunotherapies are underway. In recent studies, some of the cancer attacking immune cells were removed from patients and allowed to increase in number in a laboratory culture. Transferring larger quantities of the immune cells back to the patient resulted in additional cancer regressions. Researchers have begun exploring molecular and genetic characteristics of antigens for breast, ovarian, prostate and lung cancers, and similar treatment approaches are being applied to forms of these cancers.

NCI-funded investigators have now identified a gene that causes noninvasive, poorly metastatic melanoma cells to become invasive and metastatic. Using modern molecular technology that allows the analysis of several thousand genes at a time, the investigators examined genes expressed by mouse and human melanoma cells, some metastatic and some not, to identify genes involved in changing tumor cell behavior that might cause the cells to become highly invasive and metastatic.

This gene analysis produced several promising candidate genes, one of which is rhoC, known to be involved in tumor cell motility and invasion. When rhoC was expressed in poorly metastatic human melanoma cells, the cells became highly motile and metastatic. In contrast, when rhoC expression in metastatic cells was inhibited, the cells became less motile and were poorly metastatic. The investigators are currently testing the hypothesis that rhoC can confer metastatic properties on other human tumor cells.

Apoptosis, or programmed cell death, is a normal, gene-directed physiological process that eliminates unneeded, old, or damaged cells. Selected genes regulate a cascade of signaling pathways in the cell, causing targeted cells to stop dividing and commit suicide. This process is important to embryonic development, the daily maintenance of body systems, and the prevention of cellular overgrowth. Its disruption, however, contributes to many diseases, including cancer. For example, a mutation can occur in a gene that induces apoptosis, thwarting the signal to self-destruct. Without this signal, malignant cells can be allowed to grow unchecked. Apoptosis is currently the focus of intense interest by cancer researchers who hope that a better understanding of this process will help to explain how cancer arises and point the way to the development of new treatment strategies.

NCI-supported investigators have discovered a gene that appears to be a critical regulator of apoptosis and to be particularly important in cancer. This gene, named survivin, is the smallest member of a family of genes known as apoptosis inhibitors. The investigators have demonstrated that survivin is abundantly expressed in many malignant tumors, including basal and squamous cell skin cancers, metastatic melanoma, and bladder cancer. However, it is not expressed in normal tissue adjacent to the tumors.

The researchers have also shown in model tumor cell lines that blocking survivin expression results in spontaneous apoptosis. A recent genomic analysis found that survivin was invariably expressed in cancer but not in normal tissues. Other data suggest that survivin plays a key role in cell development by preventing apoptosis during cell division. When it is overexpressed, however, as it is in cancer cells, its anti-apoptosis function may allow cells that should have been destroyed to proliferate. Another line of investigation has shown that survivin is highly expressed in the newly formed blood vessels of tissue that forms over a healing wound. The growth of new blood vessels, or angiogenesis, is essential for tumor growth.

These findings suggest that survivin holds promise both as a marker of cancer progression and as a possible target for therapeutic intervention. Because survivin appears to have an anti-apoptosis function, blocking its expression could hypothetically promote apoptosis in cancer cells. In addition, since survivin seems to play a key role in angiogenesis, blocking its expression could inhibit the blood-vessel development that is essential for tumor growth. A next step would be to test these approaches in animal models, and if they continue to show promise, in clinical trials.

Item

Neurofibromatosis (NF) – . . . . The Committee encourages NCI to strengthen its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation and clinical trials. (p. 124)

Action taken or to be taken

Please refer to pages NCI-66 through NCI-69 of this document for NCI's response to this significant item regarding Neurofibromatosis.

Item

Neurological Cancer – The Committee is pleased to learn of innovative research on the uniformly fatal brain cancer glioblastoma multiorme. Investigators have developed a transgenic mouse model in which tumor growth can be reduced by replacing a new gene that helps transport the brain chemical glutamate. The Committee is also aware of the importance of this research in the study of epilepsy. The Committee encourages the NCI to take note of these exciting developments. (p. 124)

Action taken or to be taken

Please refer to pages NCI-81 through NCI-91 of this document for NCI's response to this significant item regarding Neurological cancer.

Item

Pancreatic Cancer – The Committee commends NCI for its report on the Pancreatic Cancer Progress Review Group. The Committee urges the NCI to develop a professional judgment budget in line with the Progress Review Group for the period from fiscal year 2003 to fiscal year 2008. **This budget should be presented to the Committee by April 1, 2002.** In addition, the Committee encourages NCI to develop an initiative to raise the awareness of pancreatic cancer in the general public and the research community. (p. 124)

Action taken or to be taken

In July, the NCI convened a meeting of the PRG to discuss the recommendations in the report and to identify strategies for addressing them. Following the meeting, the Institute prepared a 10-point action plan to accelerate and increase research on pancreatic cancer. The plan addresses each of the PRG's priorities, which include training of researchers, availability of tissue samples, identification of markers for early detection of disease, and patient and provider education. The NCI is aggressively promoting the action plan to the scientific community and to patient advocates. The response from the PRG has been very enthusiastic thus far. The action plan is posted on the Institute's Web site at:
http://osp.nci.nih.gov/Prg_assess/PRG/PANPRG/pprgannounce.htm

The Institute has created a working group of pancreatic cancer experts to translate the 10-point plan into a detailed implementation plan. Composed of staff from across the Institute, the working group will prepare the plan and oversee and track implementation.

The Institute plans to report back to the PRG in three years. This report will describe NCI's progress in implementing the plan, and it will discuss progress against the disease. Some additional specific efforts that may be of interest to the Committee include the following:

Epidemiologic research is being conducted to identify factors that play a role in the etiology of pancreatic cancer and contribute to the high rates experienced by African Americans. Because of the poor prognosis for this cancer, many previous case control studies have been based largely on interviews with proxy respondents, who often can't provide detailed information on relevant environmental exposures. To address this weakness, NCI intramural scientists conducted a population-based, case-control study in the United States based exclusively on direct subject interviews with more than 500 cases and 2100 controls. This study is one of the largest population-based, case-control studies of pancreatic cancer to include only direct interviews. Our findings have solidified the causal link between cigarette smoking and risk of pancreatic cancer. Our results also indicated that consumption of alcohol at levels typically consumed by the general U.S. Population is probably not a risk factor for pancreatic cancer, but heavy alcohol drinking may increase risk. Both black men and women had significantly higher risks associated with heavy alcohol drinking than whites.

Further, the study found that obesity is a risk factor for pancreatic cancer and appears to contribute to the higher risk among blacks than whites in the United States, particularly among women. Diabetes mellitus was found to be a risk factor for pancreatic cancer, as well as a possible complication of the tumor. The data are consistent with a key role for hyperinsulinemia and insulin resistance in pancreatic carcinogenesis, particularly among non diabetics with elevated body mass index. With regard to the black excess of pancreatic cancer, we found that established risk factors (mainly cigarette smoking and diabetes mellitus) explained almost the entire black/white disparity in incidence among men. Among women, however, other factors appear to contribute to the racial disparity, notably moderate/heavy alcohol consumption and elevated body mass index.

The NIDDK research portfolio complements NCI's particularly well in that it supports research on all aspects of pancreatic development, including studies on beta cell development with a focus on diabetes. The Institute recently co-sponsored a two-day workshop on "Pancreatic Development, Proliferation and Stem Cells" bringing together investigators from multiple disciplines working on developmental biology of the pancreas, islet cell biology and stem cells. NIDDK also supports a Beta Cell Biology Consortium that is developing mouse models and reagents useful for understanding normal pancreatic lineage and the regulation of pancreatic gene expression, and for facilitating the identity, characterization and purification of potential pancreatic stem/progenitor cell populations. The genomics effort directed at islets involves identifying all genes expressed at various developmental stages of islets. Many of these early precursors of the islet are also precursors of the pancreatic ductal cells from which most cancers arise.

The NIDDK met with the pancreas research community in March 2000 and discussed approaches to advancing research in the areas of pancreatitis and pancreatic cancer. This meeting and subsequent interactions with the community have led to several initiatives focusing on pancreas research, including a Program Announcement soliciting innovative developmental

research grants (R21s), a Request for Applications for genome anatomy projects for progenitor cells specifically of the gastrointestinal tract, pancreas and liver, and a large ongoing initiative in developmental biology of the pancreas and pancreatic progenitor stem cells. Other efforts focus on attracting new investigators and increasing research training and career development in pancreas research.

Item

Prostate Cancer - The Committee is aware of a novel DNA-based tumor vaccine that has proven effective in pre-clinical, Phase I and Phase II studies for the treatment of advanced prostate cancer. The Committee is also aware of complementary research in prostate cancer treatment using Cox-2 inhibitors. The Committee encourages NCI to explore the use of these important research initiatives. (p. 125)

Action taken or to be taken

Please refer to pages NCI-74 through NCI-80 of this document for NCI's response to this significant item regarding Prostate cancer.

FY 2002 Conference Appropriations Committee Report Language (C. Rpt.107-342)

Item

Genomics Projects - The conferees urge NCI to continue supporting cancer genomics projects with the goal of identifying potential cancer therapies. (p. 89)

Action taken or to be taken

The NCI is greatly encouraged by the excellent progress made in its' cancer genomics program. Starting in 1997, the NCI initiated the Cancer Genome Anatomy Project (CGAP), to build a platform for discovery efforts in cancer detection, diagnosis, and therapeutic development. (CGAP) is a multi-initiative NCI program to build a complete profile of genes expressed in normal, precancerous, and cancer cells. This resource is helping investigators to:

- Elucidate major steps of tumor development
- Develop molecular diagnostic techniques
- Identify molecules that can be used for early detection or drug discovery

Researchers throughout the world have used CGAP to identify molecular signatures of prostate, colon, ovary, breast, pancreas, brain, and other cancers.

CGAP consists of several interrelated initiatives that are integrated in a common database. These include:

- The Tumor Gene Index (TGI), containing more than five million gene-based DNA sequences, is the most complete public catalog of gene expression for human cancers and for mouse models of cancer. Scientists already are using TGI to classify tumors according to their molecular features for improved cancer prevention, early detection,

diagnosis, and treatment strategies. Through TGI we hope to build a complete index of cancer-related genes.

- The CGAP Genetic Annotation Initiative (GAI) has characterized and cataloged more than 30,000 human genetic polymorphisms. Polymorphisms are variations, sometimes quite subtle, in the DNA sequences of a gene that may affect its function. The GAI provides scientists with insights about genetic variants associated with certain cancers and those that occur more frequently in some populations.
- The Cancer Chromosome Aberration Project (cCAP) was established by CGAP to generate a "Human Cancer Chromosome Aberration Map" - a genetic map that defines distinct chromosomal alterations that lead to cancer. Investigators are using a molecular tool known as BAC (bacterial artificial chromosomes) clones. In 2001, cCAP passed a major milestone by producing an online version of the Mitelman Database of Chromosomal Aberrations in Cancer, a well-established and exhaustive reference of chromosome changes in human tumors. In Fiscal Year 2002, cCAP will complete a map that integrates structural mapping of the human genome with chromosomal maps.

Based on CGAP's success in building extensive databases in cancer genomics, the NCI has initiated several applied genomics programs to improve cancer detection, diagnosis, and therapy. The Early Detection Research Network (EDRN) is a research program aimed at the discovery and development of novel biomarkers for all cancers and for precancerous lesions. EDRN scientists work to further refine molecular signatures of cancer (the signposts of a cell's progression toward cancer) and to harness their uniqueness. Through these efforts, signatures become molecular tools or "biomarkers' that can be used for cancer screening and detection.

Separate EDRN laboratories cooperate to streamline the development, validation, and clinical testing of promising biomarkers and technologies for cancer screening and detection. This comprehensive, collaborative approach merges genetic pursuits with protein approaches, providing a systematic view of how the molecular signatures of specific cancers can be used as unique, identifying markers.

EDRN researchers have discovered biomarkers for the early detection of several types of cancer, including breast, esophageal, and prostate. In breast cancer studies, researchers are hoping to develop a noninvasive detection test for breast cancer based on proteins present in nipple aspirate fluid (NAF). NAF circulates in the breast ducts and contains proteins produced by the breast. An easily extractable fluid, NAF may provide a "snapshot" of the breast environment. Using a protein chip-based approach and incorporating detection with mass spectrometry, investigators have identified differences in proteins in NAF samples from a cancerous breast compared with a normal breast in the same patient and are now testing the validity of this approach with a large number of specimens.

Other studies are exploring new approaches to detect esophageal cancer at its earliest stages, when the disease is most amenable to intervention. Preliminary EDRN data suggest that gene microarrays may be used to detect premalignant and malignant esophageal lesions with a high degree of accuracy. If validated, these expression profiles offer the potential of classifying esophageal lesions by their aggressiveness and by their responsiveness to chemoprevention.

Tumors have traditionally been classified according to structural characteristics and not on molecular features that would better predict their biological behavior, treatment response, and prognosis.

Through the Director's Challenge: Toward a Molecular Classification of Tumors initiative, investigators are developing profiles of molecular alterations in human tumors using DNA, RNA, or protein-based analysis technologies. This initiative will enable researchers to develop a more clinically predictive and useful classification system for diagnosing cancer.

These efforts will shift the focus of tumor classification from structure to molecular-based schemes which may be used to define clinically important subset of tumors, helping health care providers choose the best individual prevention and treatment options.

Director's Challenge teams are working on many cancers including breast, prostate, lung, brain, ovary, colon, and leukemia and lymphoma. One team is working to subclassify node-negative breast cancer patients. Node negative/positive is a traditional classification based on whether cancer can be detected in local lymph nodes. While it is known that node positive patients have a considerable risk of cancer recurrence, this classification scheme cannot predict this risk for node negative patients. This molecular subclassification appears to address this problem and researchers are working to validate their findings for use in a clinical setting.

In FY 2001, the NCI initiated an innovative new program, the Cancer Molecular Analysis Project (CMAP). The goal of the CMAP is to enable researchers to identify and evaluate molecular targets in cancer based on extensive cancer genomics datasets. Using glioblastoma as a first example, NCI scientists are integrating the CGAP databases with state of the art information about molecular targets of cancer, molecularly targeted agents, and clinical trials.

Based on early success in these and other programs the NCI is very encouraged about the potential of cancer genomics research to facilitate the discovery of new, targeted cancer therapies.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2001 Amount Authorized	2002 Estimate	2003 Amount Authorized	2003 Budget Estimate 1/
Research and Investigation	Section 301	42§241	Indefinite	$4,145,638,000	Indefinite	$4,650,115,000
National Cancer Institute	Section 417B	42§285	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	64,083,000	b/	74,390,000
Total, Budget Authority				4,209,721,000		4,724,505,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2002 (P.L. 107-116).

b/ Reauthorizing legislation will be submitted.

1/ Reflects proposed transfer to other NIH Institutes and Centers.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1994	$2,142,122,000	$2,082,267,000	$2,082,267,000	$2,076,382,000
1995	1,967,709,000	1,917,929,000	1,917,929,000	1,919,419,000 2/
Rescission				(5,600,000)
1996 3/	1,994,007,000 3/	2,251,084,000	2,184,467,000 3/	2,251,084,000
Rescission				(2,654,000)
1997 3/	2,060,392,000 3/	2,385,741,000	2,102,949,000 3/	2,381,399,000 4/
1998 3/	2,217,482,000 3/	2,513,020,000	2,558,377,000	2,547,314,000
1999	2,528,760,000 3/6	2,787,830,000	2,927,187,000	2,927,187,000
Rescission				(1,940,000)
2000	2,732,795,000 3/	3,163,417,000	3,286,859,000	3,332,317,000
Rescission				(17,763,000)
2001	3,249,730,000 3/	3,505,072,000	3,804,084,000	3,754,456,000 5/
Rescission				(2,005,000)
2002	4,177,203,000	4,146,291,000	4,258,516,000	4,190,405,000
Rescission				(2,054,000)
2003	5,122,111,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes enacted administrative reductions of $901,000; $116,000; and $1,482,000.
3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
4/ Excludes enacted administrative reductions of $1,095,000 and $38,000
5/ Excludes enacted administrative reduction of $781,000
6/ 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 (FTEs)

OFFICE/DIVISION	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Office of the Director	769	812	822
Center for Cancer Research	1,476	1,560	1,579
Division of Cancer Biology	49	53	54
Division of Extramural Activities	98	104	105
Division of Cancer Treatment and Diagnosis	196	207	210
Division of Cancer Prevention	98	104	105
Division of Cancer Control and Population Sciences	132	140	141
Division of Cancer Epidemiology and Genetics	161	170	172
Total, NCI	2,979	3,150	3,188
Statutorily-ceiling exempt FTEs not included above	(3)	(3)	(3)
Funds to support these FTEs are provided by Cooperative Research and Development Agreements			

FISCAL YEAR	Average GM/GS Grade
1999	11.2
2000	11.2
2001	11.3
2002	11.3
2003	11.3

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Detail of Positions

GRADE	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
ES-6	1	1	1
ES-5	5	5	5
ES-4	3	3	3
ES-3	1	1	1
ES-2	1	1	1
ES-1	1	1	1
Subtotal	**12**	**12**	**12**
Total - ES Salary	$1,581,059	$1,650,665	$1,701,836
GM/GS-15	256	272	275
GM/GS-14	330	350	354
GM/GS-13	302	319	323
GS-12	428	454	459
GS-11	249	264	267
GS-10	18	19	19
GS-9	233	247	250
GS-8	149	159	160
GS-7	155	164	166
GS-6	45	48	49
GS-5	36	38	39
GS-4	28	30	31
GS-3	8	8	9
GS-2	2	2	2
GS-1	2	2	2
Subtotal	**2,241**	**2,376**	**2,406**
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	2	2	2
Director Grade	52	52	52
Senior Grade	26	26	26
Full Grade	11	11	11
Senior Assistant Grade	2	2	2
Assistant Grade	1	1	1
Subtotal	94	94	94
Ungraded	789	834	844
Total permanent positions	2,297	2,429	2,458
Total positions, end of year	3,136	3,316	3,356
Total full-time equivalent (FTE) employment,end of year	2,979	3,150	3,188
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$131,755	$137,556	$141,820
Average GM/GS grade	11.3	11.3	11.3
Average GM/GS salary	$63,285	$66,071	$68,119

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
New Positions Requested

	FY 2003		
	Grade	Number	Annual Salary
Bio Lab Tech	GS 9	1	45,261
Bio Lab Tech	GS 7	2	36,986
Biologist	GS 12	1	65,033
Biologist	GS 11	2	54,524
Biologist	GS 9	2	45,261
Chemist	GS 12	1	65,033
Chemist	GS 11	2	54,524
Chemist	GS 9	1	45,261
Clinical Outreach Program Director	GS 13	1	77,400
Computer Specialist (Informatics)	GS 13	1	77,400
Epidemiologist	GS 13	1	77,400
Geneticist	GS 15	1	115,663
Health Science Administrator	GS 14	1	94,458
Investigator (Tenure Track)	AD -	2	88,779
Lab Manager	GS 9	1	45,261
Medical Officer	GS 14	1	94,458
Medical Officer	GS 13	1	77,400
Medical Technologist	GS 9	1	45,261
Microbiologist	GS 12	1	65,033
Microbiologist	GS 11	2	54,524
Molecular Biologist	GS 14	1	94,458
Molecular Biologist	GS 12	2	65,033
Office Automation Clerk	GS 4	1	24,145
Procurement Tech	GS 7	1	36,986
Research Nurse	GS 12	1	65,033
Secretary	GS 5	1	28,696
Senior Clinical Investigator	GS 14	2	94,458
Senior Research Chemist	GS 15	1	115,663
Senior Research Geneticist	SBRS	1	155,841
Senior Research Virologist	SBRS	1	155,841
Total Requested		38	