DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

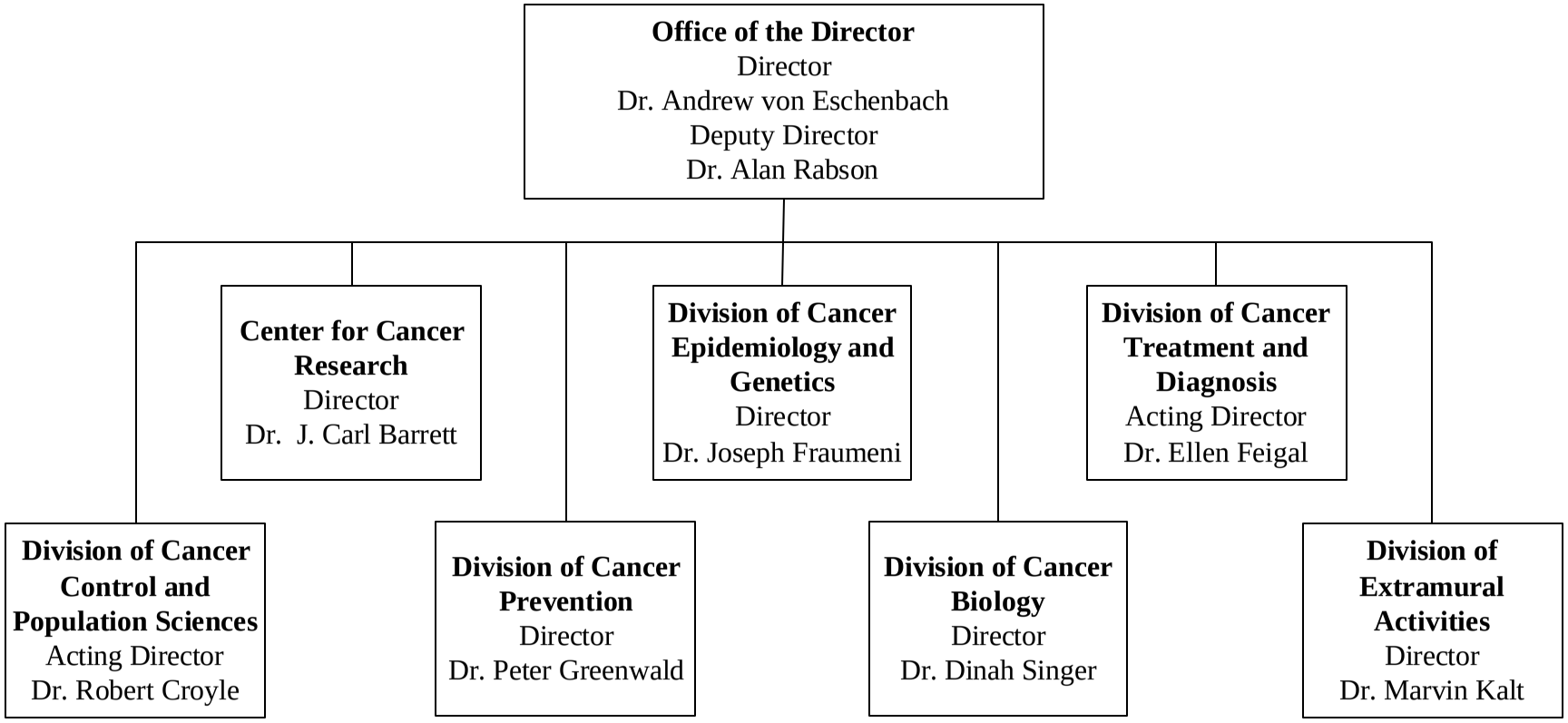
National Cancer Institute

FY 2004 Budget — Page No.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer, $4,770,519,000.

Justification

National Cancer Institute

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

Budget Authority:

FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
3,057	$4,113,673,000	3,141	$4,608,985,000	3,090	$4,770,519,000	(51)	$161,534,000

This document provides justification for the Fiscal Year 2004 activities of the National Cancer Institute, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

We as a nation stand at that defining moment in history when a surge of new technologies and the fruits of many years of investigation are resulting in giant leaps forward in our understanding of tumor biology, leading to the exciting possibility of eliminating and even preventing cancer. As President Bush noted in his call for increased funding for cancer research, "Our progress against cancer is dramatic. We know that focused and sustained efforts can make a huge difference." Progress is already measurable: overall cancer death rates decreased from 1993 to 1999 by nearly six percent and incidence rates stabilized. More people are getting screened for breast, cervical, and colorectal cancers, and more practitioners are adopting state-of-the-art cancer treatments.[1] But while we face a future filled with hope, we are immersed in a reality where more than 1.3 million Americans will develop cancer and more than 500,000 will die this year. The rates of several cancers – including non-Hodgkin's lymphoma, melanoma, cancers of the liver and esophagus, and breast and lung cancer in women – are still rising. And we still need greater efforts to fight cancer risk factors such as tobacco use, weight gain, and sun exposure, and to promote physical activity.

Because of our growing population and the greater proportion of older persons, researchers expect the cancer burden in the United States to grow substantially over the next several decades. We must require more aggressive and comprehensive strategies for cancer prevention, early detection,

[1] See NCI's *Cancer Progress Report* at progressreport.cancer.gov and *The Annual Report to the Nation on the Status of Cancer, 1973-1999, Featuring Implications of Age and Aging on U.S. Cancer Burden* prepared by 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.

treatment, social support, and palliative care, and we must continue to improve general medical services and clinical trial design and enrollment focused on the needs of older patients.

New scientific and technological advances require that we: (1) use an integrated systems approach to better understand the entire spectrum of factors that influence the initiation, development, and progression of cancer; (2) find new and more effective ways to collaborate aggressively inside and outside of the National Institutes of Health; (3) ensure the application of our research knowledge to the care of cancer patients and survivors; and (4) redouble our efforts to eliminate disparities by ensuring that every American, regardless of race, income, age, or gender, has access to high quality and timely cancer prevention, screening, diagnosis, and treatment.

We must accelerate the engine of scientific **discovery**; translate knowledge gained about the genetic, molecular, cellular, environmental, and behavioral basis of cancer into the **development** of interventions to detect, diagnose, treat, and prevent cancer; and ensure that these interventions are **delivered** to all who need them. For example, continued discovery to better understand the genetic alterations associated with the development of pancreatic and other not-yet-well-understood cancers is required. More translational research related to the prevention and cessation of tobacco use by children and youth that optimizes interventions to reduce high rates of smoking at early ages is necessary. Scientists like those on the Interdisciplinary Research Teams for Molecular Target Assessment who study critical biological processes that will uncover high priority targets for cancer drug discovery are essential. We must expedite the development of drug research capabilities through initiatives such as the Rapid Access to NCI Discovery Resources program. Partnerships with other agencies help ensure that new agents are evaluated against the full range of cancers for which they may be effective – and in combination with treatments such as surgery, radiation therapy, or other drugs. And we must ensure the delivery of these interventions for application in the clinic and public health programs by enhancing cancer communications efforts, improving access to clinical trials, accelerating the rate at which clinical trials are completed, and expanding the capacity of our Cancer Centers, networks, and consortia to disseminate proven interventions into communities and populations so that they are available to help all who need them.

SCIENTIFIC ADVANCES

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

Understanding Cancer

Tumor Microenvironment Contributes to Progression of Pancreatic and Breast Cancers. A hallmark feature of a cancerous tumor is its ability to invade the neighboring healthy tissue within its surrounding microenvironment. For certain tumor types, this invasion induces a "desmoplastic response" by stromal cells: the invaded tissue becomes inflamed and forms scar-like tissue known as desmoplastic tissue. Researchers are working to learn more about this response because mounting evidence suggests that stromal cells in the tumor microenvironment play a pivotal role in cancer growth and invasion. Indeed, infiltrating tumors (those that penetrate surrounding tissues as they grow) commonly consist primarily of desmoplastic tissue, and recent studies suggest that cancer cells and cells in the microenvironment interact in a dynamic and complex way, with each profoundly

influencing the behavior of the other. In light of this evidence, several **NCI Specialized Programs of Research Excellence (SPOREs)** researchers studied the desmoplastic response associated with pancreatic and infiltrating ductal breast tumors – chosen because they induce a particularly exuberant host response – to gain a better understanding of the process of invasion, the interaction between tumor and host cells, and tumor-specific differences in invasion. The scientists developed a profile of the genes expressed in cancerous and desmoplastic cells at the primary site of invasion. With this information, they constructed a novel picture of the "architecture" of gene expression in invasive pancreatic and breast cancers, which showed that the tumors consisted of several distinct types of tissue in which there was a highly ordered, coordinated process of gene expression and tumor invasion. The patterns of gene expression also suggested that an important communication occurs between the cancer cells and the cells in the neighboring desmoplastic tissue. The scientists identified some highly expressed products of the tumor cells, such as Connective Tissue Growth Factor, that may drive the desmoplastic process and explain why scar tissue is so prominent in some cancers. This research provides new insights into the host response to invasive cancer and may point to new markers for early diagnosis of pancreatic and ductal breast tumors, and for many other tumors known to have a "desmoplastic" component, including prostate cancer. In addition, it suggests a new and intriguing approach to cancer treatment – the development of new treatments that interfere with the desmoplastic response.

Scientists Identify Genetic Variations That May be Associated with Prostate Cancer. Prostate cancer is the most frequently diagnosed form of cancer and the second leading cause of cancer death among men in many industrialized countries. A critical step toward reducing the burden of this cancer is gaining a greater understanding of how it develops. Scientists already have identified several genes that seemingly increase men's risk for the hereditary and sporadic forms of this disease. However, investigators had yet to confirm the specific mutations on these genes that allow prostate cancer to develop. Recently, several **NCI Specialized Programs of Research Excellence (SPOREs)** researchers conducted careful population and family-based association studies and identified specific variations in several genes that appear to be associated with the development of prostate cancer. These genes are *HSD3B1* and *HSD3B2*, which are important in the proper functioning of androgens (a family of hormones that are believed to be involved in prostate cancer development); the gene for the androgen receptor itself; and *hOGG1*, which appears to repair DNA damage caused by free radicals in the prostate and other body tissues. These studies are the first to comprehensively evaluate the association of these genetic variations with prostate cancer. However, additional epidemiological and functional studies are needed to verify these important findings.

Researchers develop mouse model for study of melanoma risk. Several studies of humans suggest that sun exposure during childhood causes an increased risk for malignant melanoma. Melanoma is the cancer of melanocytes, the pigment producing cells of the skin, and is the most common and invasive of skin cancers. In the past, studies of melanoma in mice have been hindered by differences in the distribution of melanocytes in the skin of mice and humans. In humans, melanocytes are distributed throughout much of the skin, and in mice they occur only in hair follicles. Researchers recently developed a transgenic (having genes from another organism) mouse model that is expected to help in the study of genetic and environmental risk factors for melanoma, as well as in developing protection against sunburn. This model, called the HGF/SF model, has a melanocyte distribution more similar to humans and is prone to metastatic melanoma. Researchers showed that HGF/SF mice

exposed to a single, sun-burning dose of ultraviolet (UV) radiation at 3.5 days of age were likely to develop tumors similar to human melanoma several months or more after the exposure. Re-exposing the mice at 6 weeks of age did not increase the incidence of tumors and exposure only at 6 weeks did not induce melanoma. These results support several epidemiological studies of humans about the effect of childhood UV exposure; however, observations made in the HGF/SF mice may not translate directly to children because of differences in mouse and human skin thickness and because the human age equivalent of a 3.5-day-old mouse is difficult to calculate. Also, the predisposition of HGF/SF mice (unexposed to UV radiation) to late-onset melanoma is more similar to certain melanoma prone families than to the general human population.

Brief inactivation of the MYC oncogene could permanently restrict tumor growth. Oncogenes are genes that, either by mutation or overexpression of their normal forms (called proto-oncogenes), release the cell from its natural growth restraints and allow tumors to form. Researchers are developing strategies to inactivate specific oncogenes as a basis for treating certain cancers. However, because inactivating oncogenes will also shut down related proto-oncogenes, which frequently play a critical role in normal cells, scientists are concerned that permanent inactivation could be highly toxic. On the other hand, many believe that withdrawing the oncogene inactivation therapy would allow tumor growth to resume. To investigate this dilemma, a team of NCI-funded investigators used a transgenic (having genes from another organism) mouse model to show that brief inactivation of an oncogene may actually allow long-term tumor control. This mouse model expresses an oncogene (MYC) that makes them prone to certain bone cancers. However, the mice were engineered to express the oncogene only as long as they are not exposed to the antibiotic doxycycline (dox). This condition gives the researchers a way to turn MYC expression on and off. Investigators found that bone tumor cells in the transgenic mice transformed into normal, mature bone cells when MYC expression was inactivated by dox administration. Surprisingly, when the MYC oncogene was re-activated (by ceasing administration of dox), most tumor cells died through normal programmed cell death and fewer than one percent retained their abnormal growth properties. Although further research and model validation is needed, this work heralds the exciting possibility of effectively treating some types of cancer through brief inactivation of oncogenes.

Researchers Target Lymphatic Metastasis. Metastasis is the spread of cancer cells from the primary tumor site to distant sites in the body. Often, metastasis is first detected when a tumor forms in a lymph node that lies near the primary tumor. The better we understand how metastasis occurs, the better we will be able to prevent and treat it. The role that the circulatory system plays in metastasis has been well researched. However, largely due to technical barriers, we know much less of how the lymphatic vessels may be involved. Lymphatic vessels form a complex network throughout the body, bathing the tissues with a fluid that seeps out of the capillaries and eventually returns to the circulatory system. In a recent animal study, NCI-supported researchers used new laboratory techniques to investigate whether cancer cells use lymphatic vessels to move from the primary tumor site to neighboring lymph nodes. The researchers implanted cultured mouse tumor cells into the limbs of two groups of mice. The tumor cells were similar, except the cancer cells given to experimental mice were engineered to overexpress vascular endothelial growth factor-C (VEGF-C), a protein that stimulates the formation of lymphatic vessels. The investigators reasoned that if the lymphatic system is implicated in metastasis, the experimental mice would show the highest rates of metastases to regional lymph nodes, and indeed this was the case. Furthermore, the experimental mice did not

show increases in metastases to the lung, which typically are carried through blood vessels, not lymphatic vessels. Using imaging and other techniques that reveal lymphatic structure and function, these investigators showed for the first time that lymphatic vessels located on the periphery of the tumor were intact and functional, while those inside the tumor were not. Based on this strong evidence, the researchers concluded that it was through peripheral lymphatic vessels that the cancer was spreading. These early research findings suggest VEGF-C as a potential target for controlling both tumor growth and lymphatic metastasis. Further research is needed to show whether targeting VEGF-C would be safe and effective in humans.

Detection, Diagnosis, and Prognosis

Protein Profiling May Aid Prostate Cancer Detection and Diagnosis. The prostate-specific antigen (PSA) test has been a major factor in increasing awareness and improving patient management of prostate cancer. Because it does not reliably distinguish prostate cancer from non-cancer conditions that also can elevate PSA levels, however, its use in the early detection and diagnosis of prostate cancer is limited. In light of this, researchers have started searching for a combination or panel of biomarkers – needed because the molecular and cellular characteristics of prostate cancer are highly varied – that will accurately detect prostate cancer early in development and distinguish slow-growing prostate tumors from those that are more aggressive. In a recent study, investigators coupled a novel technique, known as a protein biochip, with an artificial intelligence learning algorithm to generate protein profiles from blood samples obtained from 82 healthy participants, 77 patients with benign prostate disease, and 167 patients with prostate cancer. Their objective was to determine whether this technique could be used to accurately distinguish men with prostate cancer from healthy men or those with benign disease. The investigators used the new technology to "train" the artificial intelligence program to look for 9 different proteins in the blood samples from the three test groups, which correctly classified 96 percent of the samples. Then, they tested the program on a second set of samples without knowing which samples belonged to each of the three categories. The sensitivity (correct identification of prostate cancer) of the new test was 83 percent, and its specificity (correct classification of cancer free patients) was 97 percent. By comparison, the specificity of PSA testing is greater than 90 percent, but its sensitivity is only about 25 percent, which results in subjecting men to biopsies as well as considerable anxiety. Although this high-throughput proteomic classification system still needs to be tested in a larger and more clinically diverse study set, it could prove to be a highly accurate and innovative approach for the early detection and diagnosis of prostate cancer.

Molecular Profiles Identify Clinical Subsets of Patients. Researchers and clinicians have long questioned why patients who seemingly have the same type of tumor have different rates of metastasis, react differently to a given treatment course, and consequently experience different outcomes. Traditionally, tumors have been classified according to their appearance under a microscope. As we learn more about the molecular attributes of tumors, however, we are coming to realize that tumors that appear the same may have quite different genetic profiles. Investigators funded through the **Director's Challenge initiative** are using comprehensive molecular analysis technologies to gather gene expression profiling data for different tumors with the hope that this information can be used in conjunction with traditional classification schemes to improve tumor diagnosis. With these technologies, the investigators are developing profiles of molecular changes in tumors that may predict clinical outcome. Recently, three separate groups of researchers using slightly different profiling methods identified several subtypes of lung adenocarcinoma that differed in

gene expression patterns and in clinical and pathological properties, including survival. The profiling also distinguished patients in stage I who are likely to be cured by surgery from those who require more aggressive treatment. Gene expression profiling may be a useful tool for discriminating primary lung adenocarcinoma from distant metastases to the lung, an important consideration in lung cancer diagnosis. Other investigators have used gene expression profiling to confirm the presence of three disease subtypes in a group of locally advanced breast cancer patients, each with different disease outcomes. These studies demonstrate that gene profiling of tumors can be a powerful, added tool for identifying clinically important subsets of patients with lung and breast tumors. In addition, profiling studies can allow investigators to evaluate new interventions in patients who may not benefit from current therapies and may lead to new therapies that target the molecular alterations found in the distinct subgroups of different cancers.

Triaging Women with Positive Pap Test Results. Every year, more than two million women in the United States receive a positive Pap smear result, but only five to ten percent of these women actually have a condition that may lead to cervical cancer. Referring all women with positive tests results for colposcopy (a more accurate diagnostic procedure) might be the safest course, but it would be costly, impractical, and anxiety producing. As a result, researchers have sought alternative approaches to managing this population of patients. Researchers recently reported findings from the ASCUS (atypical squamous cells of undetermined significance)/ LSIL (low grade lesions) Triage Study (ALTS) – an NCI clinical trial designed to find the best way to manage the mild abnormalities that often show up on Pap smears. The investigators examined whether the patient's age or amount of Human Papilloma Virus (HPV) – known as viral load – affects the performance of testing for the presence of cancer-associated strains of HPV, a promising approach for managing women with atypical Pap results. The investigators found that HPV testing was highly sensitive for detecting cervical cancer and its precursors in women whose Pap tests were positive for atypical ASCUS. HPV testing greatly reduced referrals for colposcopy among women with an ASCUS test result who were 29 years or older, confirming previous reports that the prevalence of HPV infection declines with age. Measuring a patient's viral load, however, was found to be clinically irrelevant. For patients with LSIL, HPV testing was not a promising strategy for colposcopy triage in any age range. This study suggests that HPV testing could dramatically decrease colposcopy referrals in older women with ASCUS, but not LSILs. These findings could serve as the basis for triage and management recommendations for women whose Pap smear results are positive for ASCUS.

New Molecular Test Appears Useful for Prognosis of Colorectal Cancer. Health professionals usually determine the stage of a tumor and its potential for recurrence through histopathological assessments, that is, by studying the tumor under a microscope and evaluating microscopic changes in the diseased tissue. For colorectal cancer, this information not only suggests the course of treatment but can also provide important insights about a patient's prognosis. Yet, histological evaluations are not always conclusive. For example, a significant proportion of early-stage colorectal cancer patients – who often are expected to recover – die because their tumors recur after initial treatment. For this reason, researchers are looking for new and better prognostic tools, such as biological markers, that can be used to determine a patient's prognosis. Investigators from **NCI's Specialized Programs of Research Excellence (SPOREs)** discovered in previous studies that colorectal cancer patients who are missing certain pieces of chromosomes 8 and 18 (known as allelic imbalance) tend to have a poorer prognosis. Unfortunately, scientists could not apply this information in the clinic because they

did not have the tools that would enable them to quickly and accurately measure allelic imbalance in tumor tissue. Recently, NCI SPORE investigators developed a highly sensitive and accurate assay, known as digital SNP (single nucleotide polymorphism) analysis, to measure the prognostic value of chromosome imbalances in early-stage colorectal cancers. The scientists used this test to measure allelic imbalance in the tumors of 180 early-stage colorectal patients and then followed the patients from initial surgery to tumor recurrence (an average of 5.5 years). They observed that 58 percent of patients with allelic imbalance in both chromosomes remained disease free, as did 74 percent of those with only one chromosome affected. By comparison, all patients without allelic imbalance in either chromosome were disease free after five years; routine histopathological staging would have predicted recurrence in at least some of these patients. This new, highly sensitive test appears to provide a better prognostic indicator of colorectal cancer recurrence in early-stage patients than the current standard of histopathological staging. Further research is needed to determine if this technique will be useful for other cancer sites.

Preventing Cancer

Tamoxifen and Breast Cancer Risk in Women with Inherited BRCA Mutations. In the NCI-sponsored Breast Cancer Prevention Trial (BCPT) conducted from 1992 to 1998, researchers showed that tamoxifen reduced by half the risk of estrogen receptor positive (ER-positive) breast cancer in healthy women aged 35 years or older who were at high risk for the disease. ER-positive cancers retain a receptor for estrogen and grow in the presence of this hormone. Tamoxifen is an antiestrogen that targets the estrogen-receptor (ER). At the beginning of the BCPT, women gave blood samples and were randomly assigned to receive either tamoxifen or a placebo.

Although mutations in the *BRCA1* and *BRCA2* genes are now known to increase breast cancer risk, the genes had not been cloned when the BCPT began. Whether tamoxifen reduces breast cancer risk in healthy women carrying these mutations was therefore unknown. In the current study, researchers examined DNA from blood samples of women who developed invasive breast cancer during the course of the BCPT to determine if they had inherited *BRCA1* or *BRCA2* mutations. Tumors of women with mutations in *BRCA1* and *BRCA2* differ in that *BRCA1* tumors tend to be ER-negative while *BRCA2* tumors are usually ER-positive. As expected, researchers found that in women with inherited *BRCA2* mutations, tamoxifen reduced breast cancer risk by 62 percent. There was a low frequency of ER-positive tumors among women with *BRCA1* mutations.

Hormone Replacement Therapy and Ovarian Cancer Risk. Despite many studies and meta-analyses (analyses of data from several studies), the relationship between hormone replacement therapy (HRT) during menopause and ovarian cancer risk remains unclear. Previous studies have lacked important data on dosage, formulation, and other ovarian cancer risk factors. In addition, formulations and dosage regimens have changed over time, making accurate comparisons difficult. NCI researchers analyzed 20 years of follow-up data from a large mammography screening study conducted in 29 U.S. screening centers by NCI and the American Cancer Society to assess the impact of estrogen replacement therapy (ERT) and combined estrogen-progestin replacement therapy (EPRT) on risk of ovarian cancer. Of the 44,247 women studied, 329 developed ovarian cancer during the study period. Use of ERT was found to be significantly associated with ovarian cancer, regardless of other ovarian cancer risk factors. In time-dependent analyses that adjusted for other risk factors and included relatively large numbers of long-term ERT users, risk increased significantly and consistently with

increasing duration of use, particularly for women who used ERT for 10 or more years. Women who used short-term EPRT were not at increased risk, but these results were based on only 18 women who developed ovarian cancer. Further investigation detailing duration, dose, and regimen is needed to determine the ovarian cancer risk associated with short-term and long-term EPRT and history of use of more than one type of HRT.

COX-2 Inhibitor Reduces Recurrence of Precancerous Polyps in Those with Severe Duodenal Disease. Familial adenomatous polyposis (FAP) is a genetic disease in which carriers commonly develop hundreds of polyps throughout the colon. FAP patients often develop cancer in their 30s and almost inevitably in their 40s or 50s if they are not treated. FAP patients also have an increased risk of duodenal (small intestine) cancer, and often have duodenal polyps, a precursor to cancer. Treatment of duodenal polyposis is difficult. When surgery is performed to remove adenomas, the tumors usually recur within a year. Endoscopic procedures may temporarily control local disease but do not prevent development of new disease. As a result, researchers have searched for drug therapies for duodenal disease. Previous studies of the COX-2 inhibitor celecoxib in FAP patients showed the drug reduced the numbers of colon polyps, and in 1999 the FDA approved it as an adjunct to usual care. The cyclooxygenase enzymes COX-1 and COX-2 help create hormones called prostaglandins. However, while COX-1 is needed for healthy mucosal tissue, COX-2 is produced by inflammatory and cancerous tissue, and is an early event in adenoma development. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) block both enzymes, but drugs like celecoxib block only COX-2, leaving COX-1 to perform essential tasks. Given the effectiveness of celecoxib in treating colon polyps, scientists questioned whether it might reduce duodenal adenomas. A clinical trial involving 83 FAP patients showed a significant reduction in duodenal polyps after six months of treatment twice a day with 400 mg of celecoxib, compared with placebo. This is the first study to show a clinically significant improvement in duodenal polyposis following drug treatment. Celecoxib may offer a new option for treating patients whose FAP disease includes duodenal growths, and it may be useful for patients with duodenal disease, particularly in severe cases.

Several Studies Examine the Effects of Diet on Cancer Risk. Over the years, many studies, small and large, have examined how what we eat or drink can change our risk of developing cancer. Since the information coming out of these studies is sometimes conflicting, there is a need for large cohort studies to clarify some of the findings. In several recent studies, including the Nurses' Health Study, the Health Professional Follow-up Study, and the Physician's Health Study, with tens of thousands of participants, NCI-supported investigators examined how several dietary components affect the risk of developing various cancers. One study demonstrated that multivitamins containing folate, diets high in both folate and methione (found in eggs, meats, and cheese), and avoidance of moderate to heavy alcohol use, might reduce the risk of colon cancer in women who have family history of the disease. Investigators found strong evidence that consuming about 700 mg per day of calcium can reduce the risk of developing cancer of the distal colon in both men and women. In contrast, another study clearly showed that high levels of calcium and dairy products substantially increase the risk for prostate cancer. The finding that calcium can reduce the risk of one cancer while increasing the risk of another illustrates the complexity of the interaction between diet and cancer. However, Lycopene, a component of tomatoes, particularly cooked tomato products such as tomato sauce, has been shown to provide moderate protection against prostate cancer. Further study is needed to define dietary risk

factors before clear advice can be communicated to the public. Future studies should concentrate on specific cancer subsites, population variables, and on better characterizing the dose-response relationship.

Treatment

FDA Approves Gleevec for the Treatment of Metastatic/Unresectable Gastrointestinal Stromal Tumors. In May 2001, the U.S. Food and Drug Administration (FDA) gave fast track approval to the molecularly targeted drug Gleevec™ (imatinib mesylate, formerly called STI571) for the treatment of chronic myelogenous leukemia (CML). Gleevec blocks the cancer causing effects of a genetically altered protein, BCR-ABL, commonly found in this disease. Researchers are now finding Gleevec promising in the treatment of gastrointestinal stromal tumors (GIST), a relatively uncommon cancer caused by genetic modification of another imatinib-sensitive protein (C-KIT). GIST is notoriously resistant to any kind of chemo- or radiation therapy, and is almost always fatal. Surgery is the current standard of therapy but will only cure patients diagnosed in the very early stages of the disease. In an NCI-supported clinical trial testing the efficacy and safety of Gleevec in 147 patients with advanced GIST, tumor size was dramatically reduced in 79 patients and tumor growth noticeably slowed in another 41 patients. Mild to moderate side effects to treatment were common but well tolerated, and severe reactions were few. It is too soon to know how long the drug will remain effective in GIST patients. With continued treatment, some patients began to develop resistance to Gleevec, although most patients continued to benefit for over six months. The majority of treated patients, 88 percent, were living one year after they began treatment, a remarkable finding given the high mortality of this disease. Careful studies of the molecular mechanisms of Gleevec action in GIST are needed to develop strategies for overcoming resistance to Gleevec. Clinical trials testing the use of Gleevec in treatment of CML, GIST, and over 15 other cancers are ongoing.

New Approach to Immunotherapy for Advanced Melanoma Results in Dramatic Tumor Regression. Melanoma is cancer of the melanocytes, the pigment producing cells of the skin. If detected early, it can be cured by surgery, but with standard treatments it is almost always fatal once it spreads beyond the initial site. In a recent clinical trial testing immunotherapy on melanoma patients, researchers discovered a way to enhance the immune system's natural, but weak, ability to attack cancer cells. Investigators began by collecting a small number of white blood cells from the tumors of each of 13 patients. From these, they identified and isolated pre-existing cells that were adept at attacking melanoma – those that could best recognize an antigen[2] abundantly expressed on melanoma cells and to a lesser extent on normal melanocytes. They grew large quantities of these white blood cells in cell culture and injected them back into each patient along with an immune-boosting protein, interleuken-2. To prevent the patient's naturally occurring white blood cells from crowding out the melanoma-attacking cells, investigators temporarily depleted the patient's immune system with chemotherapy prior to injection. With this treatment regimen, six patients experienced dramatic regression of metastatic tumors. Surgeons removed remaining traces of tumors from two of these patients who have remained cancer-free, one for over two years. In some patients, the melanoma-killing cells also attacked normal melanocytes, resulting in patches of skin without pigmentation (a non-threatening condition known as vitiligo). Other side effects were treatable. This pioneering study establishes two landmark principles of cancer research. First, this unique approach to harnessing the immune system

[2] An antigen is a protein or protein fragment located on the outside of a cell.

can be an effective treatment for patients with metastatic cancer. Secondly, naturally occurring antigens that are over-expressed on cancer cells may provide useful immunotherapy targets for cancers such as prostate, breast, ovarian, and thyroid, since the organ function is either not necessary for survival or can readily be replaced.

Patient-Specific Vaccines Help Fight B-Cell Non-Hodgkin's Lymphoma. Non-Hodgkin's lymphoma (NHL) is a cancer of lymphocytes, a type of white blood cell that defends the body against infection. There are two types of lymphocytes, B-cells and T-cells, which play different roles in the immune system. Most NHL patients have B-cell lymphoma. With standard radiation and chemotherapy treatments, about 75 percent of NHL patients survive at least a year. However, most patients ultimately relapse and only 53 percent survive five years after diagnosis. In the search for more lasting treatments, custom designed "antigen-specific vaccines" are showing promise against B-cell NHL. The vaccine is custom made in the laboratory to match the unique protein signature of each patient's cancer cells. Given to the patient after a course of chemo- or radiation therapy, these vaccines have been shown to sensitize, or "teach" the immune systems to recognize protein fragments (or antigens) attached to the outside of residual lymphoma cells. Patients with the least residual disease after standard therapy have responded best to the vaccine, achieving prolonged remission and surviving significantly longer than patients who do not respond. Researchers reasoned that pre-treating patients with myelyoablative therapy, which minimizes residual disease, might improve the effectiveness of these vaccines. Myeloablative therapy consists of high-dose chemotherapy followed by autologous bone marrow transplantation[3]. This procedure destroys and reestablishes the patient's bone marrow, dropping lymphoma cells to below detectible levels in the process. However, scientists were not sure whether patients would be capable of mounting an immune response, to the vaccine or otherwise, soon after this intensive therapy. To address this uncertainty, NCI-funded researchers treated 12 patients with relapsed or resistant B-cell NHL with antigen-specific vaccination within one year of having received myeloablative therapy. All patients had aggressive disease and would have been given a poor prognosis with standard therapy. The vaccine was well tolerated in all patients. Ten patients mounted an immune response against the vaccine, and 7 experienced prolonged remissions lasting from 3 to more than 11 years from the time of myeloablative therapy. Although further research is needed, this study demonstrated the feasibility and safety of antigen-specific vaccination following myeloablative therapy in B-cell NHL patients.

Researchers explore use of radiation therapy, with and without tamoxifen[4], after lumpectomy. During the 1980s, improved mammographic screening techniques enabled physicians to detect very small, otherwise indistinguishable, but invasive breast tumors. During the same time frame, scientists established the benefits of both radiation and tamoxifen (for estrogen sensitive tumors) therapy for preventing recurrence of these "occult" tumors. As the use of lumpectomy followed by radiation became widespread for treating women with occult breast tumors, physicians and women began to question whether the radiation component was truly helpful when tumors were less than one centimeter (less than half an inch) in diameter. At that time, the risk for tumor recurrence was

[3] Bone marrow transplant that uses the patient's own bone marrow, withdrawn before chemotherapy and preserved.
[4] This study included patients with estrogen receptor-positive and estrogen-receptive negative tumors. Tamoxifen was given to, and the data include results from, both of these groups. However, research has shown that tamoxifen is effective only against estrogen-receptor positive tumors.

believed to depend on tumor size, the smaller the tumor, the smaller the risk. Many also wondered whether tamoxifen might be just as effective, perhaps better, than radiation treatment for preventing tumor recurrence. An NCI-funded clinical trial was initiated in 1989 to study risk of tumor recurrence (primarily in the same breast) after lumpectomy in conjunction with radiation and/or tamoxifen treatment. The investigators recently reported that, overall, women with smaller tumors did not have a lower risk of recurrence. In fact, for unknown reasons, the women with the smallest tumors had a slightly greater risk of recurrence. This study also established that radiation therapy after lumpectomy indeed helps prevent tumor recurrence in the same breast. When the treatments were used singly, radiation therapy worked even better than tamoxifen. However, radiation therapy in combination with tamoxifen worked best for women with estrogen sensitive tumors. About 13 percent (45 out of 334 patients) of women given tamoxifen after lumpectomy developed a second tumor in the same breast, compared to about 7 percent (23 out of 332) of those given radiation, and close to 3 percent (9 out of 334) of those who received both tamoxifen and radiation. Tamoxifen also decreased tumor development in the second breast; about 2.2 percent of women receiving tamoxifen developed such tumors, compared to 5.4 percent in women not treated with this drug. Even so, in light of possible adverse effects including rare but serious side effects, the investigators do not recommend generalized use of radiation treatment, with or without tamoxifen, after lumpectomy for occult tumors. Instead, treatment decisions should consider the risk of recurrence for individual patients, weighing possible benefits of the therapy against potential undesirable effects. Researchers hope that, one day, tumor profiling using gene expression array technology will make this complex patient-specific analysis more straightforward and precise.

Story of Discovery

Harnessing Apoptosis to Destroy Cancer Cells

In 1972, John Kerr, Andrew Wyllie, and Alistair Currie published a paper describing a little known and curious form of cell death that today is one of the most intensively studied topics in modern biology. They reported on programmed cell death, which they labeled "apoptosis," noting that it was distinctly different from the long recognized cell death process known as necrosis. In necrosis, a cell ruptures, causing inflammatory cells to rush in to clear away the debris.

Apoptosis, however, is clean and quick: a cell shrinks and is rapidly digested by neighboring cells. Although biologists have long known that apoptosis is important in embryogenesis, Kerr, Wyllie, and Currie were the first to observe that it also occurs in mature cells. They also were the first to hypothesize that its failure contributes to a variety of diseases, including cancer.

Unfortunately, this groundbreaking paper created little excitement in the scientific community until more than ten years later when Nobel prize winner H. Robert Horvitz used the microscopic roundworm, C. elegans to explore how a single fertilized egg develops into an adult organism. As he painstakingly followed each of the developing worm's 1,090 cells to their ultimate fate, he was surprised to see that 131 cells died via apoptosis as the worm matured into adulthood.

With this observation, he substantiated the prediction made by Kerr and his colleagues that apoptosis occurred beyond embryogenesis. By 1986, Horvitz determined that three genes were responsible for

regulating apoptosis in C. elegans and demonstrated for the first time that this process is genetically programmed. Horvitz and his colleagues also determined that these genes are broadly conserved among plants and animals, indicating that apoptosis has been sustained through evolution and has a universally important biological function. These findings greatly energized apoptosis research. Over the next 15 years, scientists confirmed that apoptosis plays a central role in developing organisms by shaping neural and immune systems and molding tissue specificity, and in mature organisms by establishing a natural balance between cell death and renewal as it destroys excess, damaged, or abnormal cells.

Additional studies have revealed that apoptosis occurs through two distinct cellular pathways, one of which is initiated by signals outside the cell, the other by signals from within. Both pathways converge inside the cell, turning on a central executioner family of proteins known as caspases. Caspases act as knives, cutting up proteins inside the cell and digesting the cell from within. Because caspases become activated early in apoptosis and irreversibly launch a cell's death machinery, scientists sought their trigger. In 1996, Xiaodong Wang and colleagues discovered that caspases are activated by cytochrome c, a critical protein component of the mitochondria (the energy-producing structures of cells). With this finding, scientists began to study the mitochondria to determine how apoptosis functions in the cell, and malfunctions in disease.

Connecting Failed Apoptosis and Cancer

The link between apoptosis and cancer was not established until 1988 when David Hockenbery and colleagues characterized the bcl-2 gene. Bcl-2 was first discovered in B cells (an immune cell) from patients with follicular lymphoma (an immune system cancer). Hockenbery determined that the normal bcl-2 is a suicide "brake" gene - it produces a protein that blocks apoptosis. In lymphoma patients, the abnormal form of the gene is overactive, causing the anti-apoptosis protein to be overproduced. Cancer develops as more and more B cells are generated and fail to die. This finding, a milestone in cancer research, revealed that increased cell division was not the only way that tumors could develop. Cells could also become potent promoters of tumor growth by avoiding programmed cell death.

Throughout the 1990s, scientists gathered considerable information about bcl-2. They determined that increased bcl-2 protein production occurs in several cancers (B cell leukemias, lymphomas, colon and prostate cancers, and neuroblastoma) and is linked with poor disease outcome. In addition, overexpression of the bcl-2 gene may confer resistance to chemotherapeutic drugs. In 1997, scientists determined that the bcl-2 protein prevents apoptosis by blocking the release of cytochrome c from inside the mitochondria. Because resistance to the apoptosis- inducing effects of chemotherapy appears to develop from changes within the mitochondria of tumor cells, scientists now are working to develop a complete picture of how bcl-2 controls cytochrome c release so that they can improve the suicide-provoking effects of cancer treatments as well as thwart a cancer cell's ability to evade these drugs.

Although bcl-2 was the first component of the cell suicide mechanism to be identified, this dauntingly complicated process has many genetic controls. For example, the p53 protein, known as the guardian of the human genome, serves as an important tumor suppressor because it either blocks the cell

division of a genetically damaged cell or triggers apoptosis by causing damage to the mitochondria and cytochrome c release. In 55 to 70 percent of human cancers, however, genetic mutations render the p53 protein deficient and cells with DNA damage can continue to accumulate. Loss of p53 function is associated with tumor aggressiveness and resistance to anti-cancer treatments.

Evidence indicates that acquiring apoptosis resistance is a hallmark of most, and perhaps all types of cancer. As scientists learn more about how apoptosis fails in cancer, they also are gaining a greater understanding of why many tumors are resistant to the killing effects of radiation and chemotherapy, which both act by inducing cell suicide. These insights can inform efforts to overcome treatment resistance and offer important clues about targeted new drugs that encourage selective apoptosis. Researchers are exploring how apoptosis is regulated, how it might be repaired through genetic therapies, and how it can be selectively triggered, through tailored treatments, to induce suicide in cancer cells while leaving healthy cells alone.

Triggering Apoptosis with New Cancer Drugs

Clinical trials are currently underway to test the efficacy of new apoptosis-inducing drugs. Velcade, a new agent jointly developed by NCI and Millenium Pharmaceuticals, targets the proteosome, a device inside a cell that functions like a cellular "garbage disposal," removing abnormal, aged, or damaged proteins. By blocking proteosome activity, Velcade causes proteins to build up in the cell. One of these proteins is BAX. In the normal cell, the BAX protein promotes apoptosis by blocking bcl-2 activity. As BAX levels increase in response to Velcade, the cell undergoes apoptosis. Velcade may prove to be a versatile cancer treatment because it appears to be equally effective against cancers that do or do not overexpress the bcl-2 gene and seems to overcome a tumor's ability to develop chemoresistance. In a Phase II clinical trial of patients with progressing multiple myeloma, Velcade stabilized the disease in 77 percent of the trial participants. Based on this encouraging result, researchers are planning a Phase III trial to compare Velcade to dexamethasone, a chemotherapy now used to treat multiple myeloma. Other Phase II trials will determine the drug's effectiveness in treating breast cancer, non-small cell lung cancer, melanoma, sarcoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and neuroendocrine and renal cancers.

Genasense is another apoptosis-inducing agent that is being tested for its clinical use. Developed by the Genta Company, this drug blocks the production of the bcl-2 protein and leaves cancer cells more vulnerable to apoptosis-inducing chemotherapies. NCI and Genta are cosponsoring clinical trials in lung cancer and leukemia patients to determine whether pretreatment with this drug followed by state-of- the-art chemotherapies improves treatment outcome.

NEW INITIATIVES

The intricacies of cancer may be thought of as a challenging jigsaw puzzle that has many pieces. Our efforts to clarify these intricacies are akin to finding and piecing together the numerous pieces of a jigsaw puzzle to create a clear and recognizable picture. Through research, the jigsaw puzzle of cancer is beginning to take shape. However, we are still a long way from completing the final picture. Many pieces have yet to be identified, and those already identified must be properly seated into the emerging picture. The progress just described proves we are coming ever closer to solving the cancer

puzzle. And, the proposed initiatives that follow illustrate our plans for completing this challenging puzzle.

Signatures of the Cancer Cell and Its Microenvironment

Scientists have firmly established the fact that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change. These changes are unique molecular "signatures" and serve as signals of the presence of cancer. Our evolving knowledge of cellular signatures has laid the foundation for important opportunities in prevention, detection, diagnosis, and treatment. If we can accurately "read" the signature changes that distinguish a cancer cell from its normal counterpart, we can detect the changes that signal cancer at its earliest stage, more accurately diagnose a tumor according to its molecular features, and select appropriate treatments.

The cancer cell, however, is only part of the story in cancer development. As cancer develops, malignant cells interact dynamically with its surrounding local and systemic microenvironment, each profoundly influencing the behavior of the other. This "tumor microenvironment" – which is populated with a variety of different cell types, is rich in growth factors and enzymes, and includes parts of the blood and lymphatic systems – can not only *permit a tumor to grow and spread* but can also *influence the access of therapeutic agents to tumor cells, the body's processing of treatment agents, and the development of resistance to cancer treatments.* The influence between tumor cells and cells in the microenvironment is bi-directional. Because of this interaction, cells in the microenvironment often take on atypical characteristics and their behavior can change. In light of this information, physicians now realize that they confront an entity that consists of malignant cells combined with elements of the host environment when treating a cancer patient. Accordingly, we need to identify and characterize the full compendium of signature changes that occur within cancer cells and cells in their surrounding environment in order to understand how cancer grows in the body, to explore the mechanisms of how cells "cross-talk" in their normal physiological setting and how alterations in the "cross-talk" between cancer cells and normal cells in the tumor microenvironment can promote the initiation and progression of tumors, and to consider all of these elements when developing new interventions to fight cancer.

NCI already is helping scientists in the field to make important progress in this area through a variety of innovative and large-scale initiatives, including the Cancer Genome Anatomy Project, the Early Detection Research Network, the Director's Challenge: Toward a Molecular Classification of Tumors, and the Clinical and Biomedical Proteomics Programs. The Institute plans to establish initiatives that enable cancer researchers to define the molecular signatures of cells in the cancer microenvironment at various points during initiation and progression of cancer, to define the dynamic communications among cancer cells, surrounding cells, and immune cells that control or promote tumor growth, and to apply knowledge from these studies to create targeted interventions. Our long-range goal is to extend signatures research to characterize the interaction among a tumor, its microenvironment, and the entire body. All of these signatures provide important clues for understanding cancer development, detection, diagnosis, and prognosis and are important targets for prevention and treatment interventions.

Nanoscience and Nanotechnology

With a far better understanding of the molecular basis of cancer, researchers today are able to develop technologies that can detect cancer when it first develops, design drugs that target specific molecular features of cancer cells, precisely guide and monitor cancer treatments, and much more. Indeed, with emerging technologies that exploit newly gained knowledge, we are approaching a day when the norm of cancer care will be patient-tailored interventions that are minimally invasive, non-toxic, and ubiquitously effective. This "new world" of cancer prevention, detection, and treatment will be accelerated by a variety of complementary technologies from ultra-fast computers, to new machines for analyzing genes and proteins, to bedside equipment that directly benefits patients. But among all these new wonders of technology, one of the most exciting and promising is nanotechnology.

Nanoscience and nanotechnology involve the study and creation of useful materials, devices, and systems through the manipulation of matter that is less than 100 nanometers in size. For scale, a nanometer is one billionth of a meter, or 80,000 times smaller than the width of a human hair. In fact, nanotechnology devices are small enough to easily enter animal cells, which generally range about 10,000 to 20,000 nanometers in diameter.

Today, much of the science of nanotechnology is necessarily focused on *basic research*, designed to reach a better understanding of how matter behaves on this small scale. Factors that govern larger systems do not necessarily apply on the nanoscale. However, *in vitro* and *in vivo* nanotechnologies for cancer detection, diagnosis, and treatment are in various stages of discovery and development. Experts believe that devices for detection and diagnosis as well as therapeutic agents may be available for clinical use in 5 to 15 years. Devices that integrate detection and therapy could be clinically available in about 15 or 20 years.

Scientists expect highly sensitive, efficient, and cost effective nanotechnology tools to allow *cancer detection* at the stage of its earliest molecular changes, when the promise of cure is the greatest. Nano-cantilevers, an *in vitro* application, are tiny bars anchored at one end that can be designed to bind molecules altered by cancer. This binding causes changes in surface tension, which cause the cantilevers to bend, signaling the presence of cancer cells. Other technologies will focus on improved methods of reading the genetic code on single strands of DNA to detect errors that may contribute to cancer.

Quantum dots, an *in vivo* application of nanotechnology, are tiny crystals that glow when stimulated by ultraviolet (UV) light. To detect cancer, scientists can design quantum dots that bind to sequences of DNA that are associated with the disease. When the quantum dots are stimulated with UV light, they emit unique light signals akin to a bar code or label, making the critical, cancer-associated DNA sequences visible. The diversity of quantum dots will allow scientists to identify numerous regions of DNA simultaneously. This will be important in the detection of cancer, which results from the accumulation of many different changes within a cell.

For *cancer treatment*, researchers are developing synthetic spheres of molecules, or biosensors, that can enter the blood stream to locate even small numbers of cancer cells.

Biosensors are being designed to seek out and image cancer cells, provide diagnostic and prognostic information, eliminate the cancer cells on a cue from the physician, and monitor response to treatment – all with minimal side effects and little disruption of healthy tissue.

The NCI is supporting promising research in nanotechnology through several programs including the Innovative Molecular Analysis Technologies, the Unconventional Innovations Program, the Biomedical Imaging Program, and the NASA/NCI Program on Fundamental Technologies for Development of Biomolecular Sensors. In addition, we are aggressively pursuing collaboration with others who are developing nanotechnology for other scientific, medical, and industrial applications.

NCI plans to expand these existing programs to boost the research and development of biosensors for *in vivo* use and nanotechnology tools for *in vitro* and *in vivo* detection of cancer signatures and targeting of molecular features of cancer cells. A new Center for Biosensors in Oncology will be established to promote research on the integration of new biosensors systems. We will facilitate collaborations to translate emerging nanotechnologies into tools that can be used in clinical practice. Ultimately we look to a day when nanotechnology will allow cancer to be detected when it is only a few cells strong and when patients can be diagnosed, treated, and monitored with a simple injection and non-invasive monitoring rather than with surgery, chemotherapy, radiation, or other conventional therapies.

Cancer Survivorship: Improving Treatment Outcomes and Quality of Life

Entering the new millennium armed with new insights into biology, we are beginning to see the fruits of the "War on Cancer" launched in 1971. Once almost uniformly fatal, cancer has become a chronic illness for many and, for growing numbers of people, a curable disease. There are an estimated 8.9 million cancer survivors in the United States today. An impressive 14 percent of these individuals were originally diagnosed over 20 years ago. Fewer deaths from other diseases and the aging of the population also contribute to the rising number of cancer survivors. However, many unanswered questions remain about the health status and quality of life for most patients in their post-treatment years. The adverse effects of cancer treatment remain poorly documented and understood. As presently configured, our surveillance databases – e.g., Surveillance, Epidemiology, and End Results (SEER) and tumor registries – often cannot provide information about a patient's current health status and phase of survivorship, whether in active treatment, disease free, or dying of cancer.

What is clear is that most of our current treatments will produce some measure of adversity. As children and adults with a history of cancer are living longer and data from NCI research studies are maturing, the nature and extent of long-term and late effects are being documented and reported. These effects include neurocognitive problems, premature menopause, gastrointestinal system dysfunction, cardiorespiratory system dysfunction, sexual impairment, infertility, chronic fatigue and pain, second malignancies, and others. The biological mechanisms for these effects are not yet well understood. In addition, adverse effects are not limited to physical and functional problems. Research shows that survivors and their families often experience significant psychosocial problems including fear of recurrence, sense of isolation, anxiety and depression, employment and insurance discrimination, altered body image, and relationship difficulties. When we are able to identify patients at increased risk for complications of treatment and develop interventions to reduce those risks, we will be able to help patients, their families, and their providers negotiate critical decisions.

NCI is initiating a focused effort in 2004 to understand the mechanisms that affect a cancer patient's response to disease, treatment, and recovery; accelerate the pace of intervention research; develop tools to assess quality of life following treatment; track outcomes for cancer survivors; disseminate clinical guidelines; and expand the scientific base for understanding the adverse late effects of current and new cancer treatments.

Among the critical issues for cancer survivors are "late effects" of their illness and treatment that may not be apparent for a number of years. Current NCI initiatives include a program to update the common toxicity scoring system, a tool for enhancing studies on the long-term consequences of cancer treatment, to incorporate the Late Effects of Normal Tissues (LENT) score. This tool enables investigators to:

- Compare newer treatments with the current regimens for treating cancer.
- Relate laboratory research to the severity of effects experienced by patients when investigating molecular mechanisms for late tissue damage.
- Facilitate the development, for use in clinical trials, of interventions to prevent, reduce, or possibly reverse late effects of cancer treatment.

NCI will leverage research focused on our survivorship community, to improve the quality of care, control costs, and equip the next generation of physicians, nurses, and other healthcare professionals to provide not just the science but also the art of comprehensive cancer care.

The Immune System and Cancer

The immune system is a complex network of organs, cells, and cellular secretions that protects an organism from foreign substances. Its ability to distinguish between "self" – a body's healthy cells and tissues – and "non-self – substances such as viruses, bacteria, or even transformed cancer cells – enables it to maintain a constant surveillance against all foreign invaders. As a result, the system maintains the health of an organism by attacking anything foreign, including abnormal cells, while leaving the organism's own normal cells unharmed. When a foreign substance enters the body, this powerful surveillance system detects its presence and responds by specifically targeting, attacking, and eliminating the invader. Sometimes, however, a cancer cell slips past the immune system. When this occurs, the immune system not only fails to recognize the threat posed by a cancer cell, it tolerates its progression to a tumor and its spread throughout the body.

Over the last 20 years, cancer researchers have sought to exploit the strength of this natural defense system and use it as a targeted and nontoxic cancer treatment. To achieve this ambitious goal, scientists have first worked to gain a fuller understanding of how the immune system responds to cancer cells and how a tumor can thwart this response. Through these studies, investigators have determined that the immune system consists of two arms: an innate arm that provides a "first line of defense" and an adaptive arm that provides immunity tailored to a specific insult. NCI research, much of which has centered on adaptive immunity and its failure to eliminate tumors, has yielded significant insights into the mechanisms of immune surveillance, tumor molecules that are recognized by the immune system, and the immune cells that can be harnessed to destroy cancer cells. Investigators have also shown that cancer growth does not occur because of a breakdown of the immune system, as was commonly believed. Instead scientists now believe that cancer cells, which

differ only in small ways from normal cells, are not perceived as strikingly abnormal and are therefore tolerated by the immune system.

New evidence also suggests that a tumor itself plays an active role in suppressing the body's adaptive immune response. Many tumors have been shown to secrete molecules that paralyze the immune cells responsible for eliminating tumors. How a tumor interacts with immune cells and factors in the tumor microenvironment is still poorly understood. NCI plans to fund studies that will explore the dynamic communications among cancer cells, surrounding cells, and immune cells that control or promote tumor growth and characterize the interaction between the immune system and cancer cells during cancer initiation and progression.

NCI scientists are working to develop a wide range of immunotherapies designed to repair, stimulate, or enhance the immune system's response and help it recognize cancer cells as dangerous invaders.

- *Nonspecific Immunomodulating Agents*. These substances nonspecifically boost immune response. Agents already used as treatments include levamisole, which is used with the chemotherapy fluorouracil to treat advanced colorectal cancer.
- *Biological Response Modifiers*. Some immune substances and cells can be "mass produced" in the laboratory for use in cancer treatment. Collectively referred to as biological response modifiers, these factors alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease. Examples include interferon, interleukins, and monoclonal antibodies. Herceptin, a monoclonal antibody to the her-2 protein found on some breast cancer cells, is used to treat metastatic breast cancer. These factors are being developed to be used alone or in combination with chemotherapies or radiation.
- *Vaccines*. Cancer vaccines are a biological therapy designed to provoke an immune response. Evidence suggests that stimulation of T cells, a type of immune cell, produces the most effective anti-tumor immune response. Accordingly, many vaccines are developed to directly or indirectly activate T-cell response. NCI's Vaccine initiative is an important program in this promising research area. It brings together a consortium of scientists with expertise in oncology, vaccine development, and translational research along with representatives of the biotechnology and pharmaceutical industries in an effort to speed development of vaccines and facilitate their delivery to patient care. Several vaccines developed by consortium members are already being used in the clinic. Through this and other initiatives, NCI scientists are working to: define which vaccines and vaccine strategies currently available are most potent in inducing immune responses and anti-tumor activity for a range of human cancers; synergize the different approaches and technologies now available to make the next generation of cancer vaccines more effective in inducing anti-tumor responses; better define and compare patients' immune responses to different vaccines and vaccine strategies before and during clinical trials; develop improved preclinical models to study new vaccines; expedite the development of clinical trials to assess the efficacy of new vaccines for treating colorectal, prostate, breast lung, bladder, pancreatic, and various other tumors; and change the paradigm of vaccine use, that is to study the benefit of using vaccines early in treatment, perhaps before or during the use of more conventional cancer therapies.
- *Adoptive Transfer*. This new approach to cancer treatment involves replacing a patient's immune system with cancer-fighting cells. Recently, a team of NCI-scientists used this approach to treat patients with melanoma. Using white blood cells samples collected from 13 patients with metastatic melanoma, the investigators isolated the T cells that best recognized and attacked

melanoma cells. They then grew large quantities of these T cells in the laboratory. The patients were treated with agents to deplete their own immune cells, which had proven ineffective against the cancer. Once a sufficient number of T cells were available in the laboratory, the investigators injected them into the melanoma patients. Nearly half of the patients tested experienced dramatic tumor regression. Although further research on this new approach is needed, scientists hope that it will be a useful strategy for treating several types of cancer, as well as infectious diseases such as AIDS.

OTHER AREAS OF INTEREST

In recent years, NCI's has identified and developed several broad priority areas that serve as the framework for our strategic planning. Some of these priority areas focus on building and sustaining the strong research mechanisms, support structures, and collaborations that enable us to pursue rapidly evolving discoveries in cancer research. Others emphasize a focus on the broad scientific opportunities and emergent fields of research so that we can advance scientific discovery and its clinical application. And, some address cancer care and its consequences and stress the translation of research discoveries into full application for people affected by cancer.

Building the Nation's Cancer Research Capacity

Bringing the benefits of cancer research to the American people depends on building and sustaining the strong research mechanisms, support structures, and collaborations that enable us to pursue rapidly evolving discoveries. NCI must provide the vision, creative environment, and diverse resources needed to ensure a fast paced and synergistic flow of innovative thinking among scientists in disparate scientific disciplines and across the discovery-development-delivery continuum.

Enhancing Investigator-Initiated Research. To develop the concepts that lead to discovery and to translate results to targeted drugs and treatment, investigators must not only have funding but must also have access to powerful new tools, special resources, and opportunities for collaboration. NCI strives to balance the flow of resources through flexible funding options such as cooperative agreements, seed funds, and supplemental funds for unanticipated opportunities. Compelling proposals and novel approaches are supported with funding specifically set aside for innovative proposals. And NCI works to ensure that proposals from new investigators are given special funding consideration.

Expanding the Capacity of Centers, Networks, and Consortia. The rapid pace of scientific and technological discovery requires that scientists of diverse backgrounds work together to share the information and resources required to address the "big picture" problems in cancer research. We must expand the number of NCI-sanctioned Cancer Centers, networks, and consortia that serve as platforms to support new technology development; improve informatics capabilities; conduct laboratory, clinical, and population research; and disseminate state-of-the-art breakthroughs into the communities. Specialized Programs of Research Excellence (SPOREs) are integrally connected to these platforms and enable basic and clinical scientists to work together to address broad-based needs for translational research focused on specific types of cancer.

National Clinical Trials Program in Treatment and Prevention. NCI provides a versatile system to safely move emerging cancer interventions into health care delivery. This requires that we identify the most important questions that can be addressed through clinical trials. We must modernize and streamline the process of trial design, approval, and implementation. We must employ sophisticated bioinformatics infrastructure; create tissue and specimen banks; develop surrogate endpoints[5] for use in small translational trials; move the most promising interventions into large and easily accessible trials; and simplify administration activities while increasing patient accrual, to substantially increase the number of new treatments and other interventions being evaluated.

Developing Bioinformatics and Computational Biology for Cancer Research. Sophisticated, well integrated bioinformatics tools are beginning to allow scientists to take full advantage of the expanding flood of cancer-related information to conduct virtual experiments using data from multiple sources and to create and manage more knowledge faster and more effectively. We simply must be able to capture and store the disparate pieces of information coming from basic, clinical, and population research and then manipulate that information to reveal the intricate connections and systems that give rise to cancer. Bioinformatics tools are also facilitating directed cancer diagnosis, as demonstrated in the recent marriage of proteomics and artificial intelligence that resulted in a promising ovarian cancer screening test. Continued development will lead to new models and tools for bridging separate scientific vocabularies, integrating concepts and information, and enabling complex analysis.

Advancing Discovery in Cancer Research and its Application to Cancer Care

The story of cancer research involves myriad characters and plot lines. The protagonists include the researchers and clinicians who strive to understand the nature of cancer and improve cancer prevention, detection, diagnosis, treatment, and control and the people from all walks of life who are battling cancer or are at increased risk for the disease. The plots are wide-ranging and complex and feature the abnormal genes and proteins that, in their improper functioning, contribute to the development and progression of cancer. Investigators explore how elements in our environment and/or lifestyle interact with our genetic constitution to give rise to cancer and how our growing knowledge of the steps involved in tumor growth can reveal markers for early detection or a target for prevention or treatment. They translate new imaging and molecular sensing technologies to dramatically improve detection, diagnosis, and treatment. And they work to improve communication among researchers and the dissemination of new interventions into clinical application and better public health programs.

Genes and the Environment. The study of genes and the environment increases our understanding of the interplay between inherited susceptibility to cancer and environmental and life style factors, enabling the development of more effective approaches to cancer prevention, early detection, and treatment. NCI is investing in this area through large-scale collaborations that enable scientists to conduct large population studies that will unlock the full potential of new discoveries in genomics. Scientists are also working to understand additional environmental risk factors and susceptibility genes and how they interact in cancer causation; identify genes in high-risk families and investigate

[5] Surrogate endpoints are based on laboratory measurement of some biological indicator of an intervention's effectiveness, rather on longer-term outcomes such as survival or tumor regression.

how genetic and environmental factors modify them; and better understand the clinical, behavioral, and societal issues associated with cancer susceptibility.

Signatures of the Cancer Cell and its Microenvironment. Scientists realize that if we can accurately "read" the signature changes that distinguish a cancer cell from its normal counterpart, we can detect the changes that signal cancer at its earliest stage, more accurately diagnose a tumor according to its molecular features, and select appropriate treatments. And, because we now realize that seemingly healthy cells within the surrounding microenvironment are "co-conspirators" that interact with cancer cells to encourage tumor growth, we must also identify the signatures of normal microenvironment cells and those that reflect changes as cancer cells interact with the host environment. (See a more detailed discussion of this research area in the New Initiatives Section.)

Molecular Targets of Prevention and Treatment. Our ability to decipher the molecular basis of cancer has launched an exciting era in biomedical research as we hone molecular targets for the prevention and treatment of cancer. Researchers are directing a new generation of low toxicity, high efficiency agents against the specific molecular features, or targets, that cause tumor growth. NCI is exploring a variety of targeted approaches, including strategies to trigger a cancer cell to revert to normal, to stop replicating, or to self-destruct. Other strategies improve immune response to combat cancer or block the tumor microenvironment from supporting cancer growth. Future studies will further exploit potential targets, investigate the use of radiation with molecular therapeutics, and develop the next generation of cancer vaccines.

Cancer Imaging and Molecular Sensing. New imaging technology has dramatically improved cancer detection and diagnosis and is making image-guided therapy and post-treatment monitoring a reality. X-ray technology is giving way to more sophisticated scanners, like MRI spectroscopy, positron and single photon emission tomography, and optical scanning. We must now work to continuously improve functional imaging, develop molecular and digital imaging databases, build micro-imaging techniques for animal research, and support more biosensor research. Other studies will focus on expanding the development of novel imaging agents and devices that detect not only the presence of the tumor but can "see" its metabolic and biologic activity, increasing clinical trials and public-private partnerships to move promising imaging advances to the clinic, and integrating functional imaging methods into therapeutic clinical trials. Further advances will allow even earlier, more accurate, and less invasive diagnoses; more individualized treatments; and more precise patient monitoring.

Cancer Communications. Effective communication of research findings empowers people to make informed cancer-related decisions and adopt new behaviors to improve their health. NCI is working to optimize the use of communications tools while building strategies to enhance interaction between patients and health professionals and among health professionals. Lives are saved through communication interventions that decrease or prevent smoking, influence good nutritional choices, and increase the number of people who are screened to detect cancer early. NCI plans to establish new data collection and analysis strategies, accelerate the pace of research and the development of communications interventions, increase access to and use of cancer information, and improve understanding of and ability to effectively move research results into clinical practice.

Addressing Areas of Public Health Emphasis

Millions of people in our country do not receive appropriate care for their cancer, nor the support they need for dealing with the emotional, physical, and psychological effects of cancer and its treatment. Untold numbers are denied proper care because of social position, economic status, cultural or language barriers, or geographic location. In each instance, we need better science to understand the complexities and to inform aggressive policy decisions and planning for public health programs. As we study disparities, we can take action against them where the causes are clear. And there is a pressing need to address the challenges posed to our Nation's healthcare system by the rising incidence of cancer in the aging U.S. population. For all Americans, we need evidence-based interventions that will prevent cancer from occurring and improve the health and quality of life for those who are affected by cancer.

Improving the Quality of Cancer Care. Barriers to high quality cancer care, ranging from system and financial limitations to physician and patient biases, are a major national concern. NCI is helping to improve measurement of patient outcomes; support innovative research on the diffusion, quality, and outcomes of cancer interventions and its translation to best practices in patient care; enhance quality-of-care research; strengthen cancer communications; and inform science-based Federal decision making. For example, the Cancer Care Outcomes Research and Surveillance Consortium and other studies are strengthening the science base for understanding palliative care and symptom management and end-of-life distress as well as examining depression in cancer patients.

Reducing Cancer-Related Health Disparities. The U.S. healthcare system must be empowered to provide all Americans equal access to proven cancer interventions. Among progressive initiatives, NCI sponsors 18 Special Populations Networks for Cancer Awareness Research and Training that build relationships with community-based programs, foster cancer awareness activities, increase minority enrollment in clinical trials, encourage grant applications and develop junior biomedical researchers from minority and underserved communities. Collaborations with NCI Divisions and clinical/academic partnerships among Network awardees and Cancer Centers, academic institutions, and Clinical Cooperative Groups are essential to all of these activities. Other initiatives include the implementation of a landmark study to determine factors that contribute to cancer among groups hardest hit by the disease. A number of planned efforts will define and monitor cancer-related disparities; and develop and implement new policy, community, and clinical interventions, and evaluate their impact.

Cancer Survivorship: Improving Treatment Outcomes and Quality of Life. Through the fruits of the "War on Cancer" and aided by the aging of the population, we are seeing a marked rise in the number of cancer survivors. Accordingly, NCI is initiating a focused effort to understand the mechanisms of patient response to cancer treatment and outcomes experienced by the increasing population of cancer survivors. (See a more detailed discussion of survivorship research in the New Initiatives section.)

Research on Tobacco and Tobacco-Related Cancers. Tobacco use and tobacco exposure are having a devastating impact on the incidence of cancer. NCI is focusing on improving understanding of the behavioral and biologic components of tobacco-related addiction and carcinogenesis, including the role of genetic and environmental factors in smoking initiation, continuation, and relapse. Through several new initiatives, including the early detection effort of the Lung Cancer Screening Study as

well as preclinical and clinical studies to identify more potent agents for cancer prevention, NCI-supported research is targeting the health needs of current and former smokers. NCI plans to expand the infrastructure needed to conduct a vigorous research program; support investigations to understand and treat tobacco use and addiction; and apply cutting edge research to better understand and treat tobacco-related cancers.

Behavioral Factors and the Risk of Cancer. In addition to tobacco, a range of behavioral or lifestyle factors may influence cancer development. For example, we have learned that obesity increases the risk for several cancers, including colon cancer, post-menopausal breast cancer, endometrial cancer, gastric cardia, and adenocarcinoma of the esophagus. People whose diets are rich in fruits and vegetables have a lower risk for developing cancers of the lung, mouth, pharynx, stomach, and colon. Exercise may also play a role. Studies suggest that a sedentary lifestyle places one at higher risk for colon and breast cancer, and physical activity has been linked to decreased incidence of cancer as well as improved recovery and quality of life for cancer patients. In light of these findings, we must now consider the role of energy balance – how we eat, how we move, and our body shape – in the development and behavior of cancer. As with tobacco, we need to explore this issue from a behavioral and biological perspective.

The Interface of Aging and Cancer

The risk of developing cancer increases with age. By 2030, 20 percent of the U. S. population will be over 65 and the number age 85 years and older will have more than doubled in size from 4 million to approximately 8.5 million. Close to 58 percent of all newly diagnosed malignancies and 71 percent of all cancer deaths are in persons 65 and older according to the NCI Surveillance, Epidemiology, and End Results (SEER) program data for 1995-1999. In the face of these numbers, current healthcare practices frequently fall short of providing the best available early detection, treatment protocols, and quality care that older patients deserve. Studies show that older people are less likely to be screened for prevalent diseases such as breast, colorectal, and cervical cancers. In addition, older patients receive less frequent assistance for symptom control because of inadequate standards of care.

Because of the vulnerability of our Nation's aging population, NCI and the National Institute on Aging (NIA) have partnered to integrate crosscutting aging and cancer research priorities. Recommendations for engaging NCI-supported Cancer Centers in pioneering research came out of a workshop jointly sponsored by NCI and NIA. Further work is needed to fully address the interface of aging processes with cancer detection, diagnosis, and treatment; with the efficacy and tolerance of anti-cancer drugs; with survivorship and symptom control; and with disease-specific studies. Aging patients differ from younger patients in susceptibility to disease progression and response to treatment. Current and projected studies related to the aging process intersect a number of NCI priority research areas, including the underlying biological mechanisms of cancer.

- *Genes and the Environment* studies examine factors such as oxidant stress and cell death that may alter tumor progression in the aging patient.
- *Signatures of the Cancer Cell and Its Microenvironment* studies focus on the interaction of normal aging cells and cancer cells, differences among cancer types in older and younger patients, differences in response to therapy, and differences in molecular alterations related to aging cells.

- *Molecular Targets of Prevention and Treatment* studies examine which aspects of tumor biology and tumor growth vary by age. These investigations can provide information important to tailored therapeutic approaches.
- *Cancer Imaging* studies have led to an expanding array of diagnostic procedures to reduce treatment side effects and optimize recovery for older patients.
- *Quality of Cancer Care* studies link the NCI SEER cancer registry to Medicare and other insurance data to assess the quality of cancer care and survivorship for older patients. Other studies investigate current methods of symptom management, the effects of multiple health problems, and the limited functional reserve of the aging.
- The *National Clinical Trials Program* works to increase the accrual of people 65 and older to early trials and develops trials that are specifically designed for older cancer patients. Trials for new agents and toxicology models include efficacy and tolerance evaluations in the aging.
- *Survivorship* studies identify potential short- and long-term medical effects induced by treatment such as susceptibility to multiple primary tumors, anti-tumor drug alterations, and cancer recurrence.

INNOVATIONS IN MANAGEMENT AND ADMINISTRATION

Managing for Results in NCI's Business and Administrative Units

In support of the President's Management Agenda and DHHS and NCI management initiatives, in FY 2002, NCI initiated a strategic planning model for its business/management infrastructure. Each business/management unit: (1) conducted an assessment of customer needs; (2) identified its priorities in terms of measurable, mission-critical goals; (3) reported results at the end of the fiscal year; and (4) is now evaluating its goals, targets and strategies and refining them, as necessary, for FY 2003. Implementation of this model and achievement of FY 2002 targets ensured clear communication of business unit priorities, improved accountability, better customer service, and availability of information for informed budget decisions.

Information Technology Services

NCI continues to enhance information technology services for both scientific and management staff. The areas of genetics and imaging, in particular, demand significant information resources and other disciplines increasingly require storage of scientific data. The implementation of security and performance enhancements for Web sites and network operations is also of vital importance. An industry standard approach, the Rational Unified Process, is designed to decrease risk and improve software product quality for development projects.

Technology Transfer

NCI is committed to forging scientific collaborations with the private sector and academia to 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 the full scope of partnership possibilities, including:

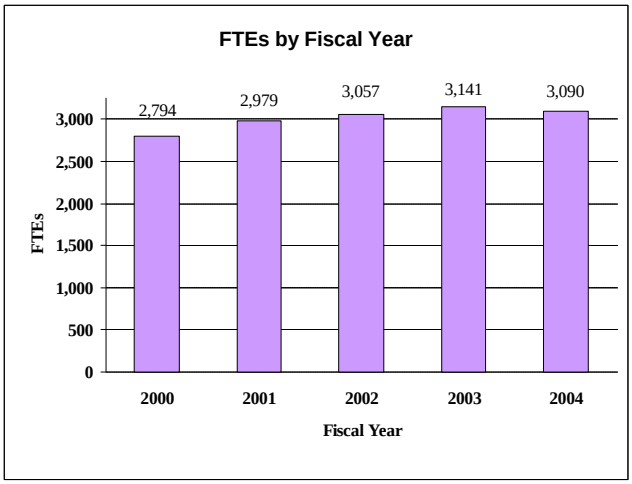
- Developing new NIH health outcome metrics for technology transfer, with the first two case studies posted on the NIH Technology Transfer Web site.
- Coordinating with the Technology Development Corporation (TEDCO) Federal Lab Program, the U.S. Army, and other NIH components to plan a joint NIH/U.S. Army technologies showcase on

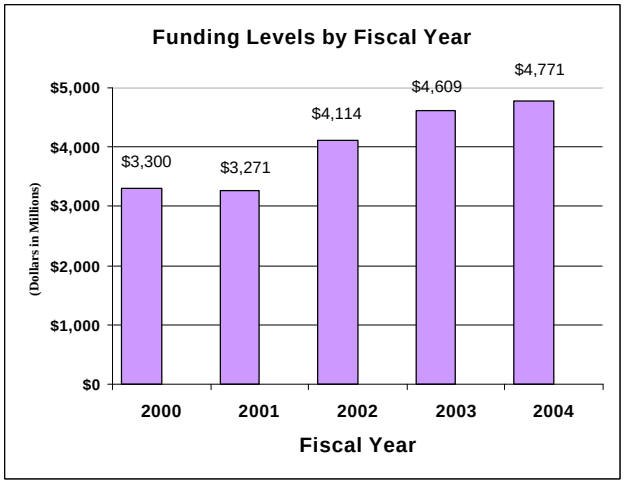
vaccines and immunotherapy collaborative opportunities.

- Highlighting collaborative research opportunities with the NCI Center for Cancer Research at the Drug Discovery Technology 2002 meeting.
- Establishing regular direct e-mail notification of Cooperative Research and Development Agreement (CRADA) opportunities.
- Developing an educational seminar on inventions, patents, licenses and royalties. As of November 1, 2002, over 400 NCI scientific scientists have taken the new NIH on-line technology transfer training.

Budget Policy

The Fiscal Year 2004 budget request for the NCI is $4,770,519,000, including AIDS, an increase of $161,534 and 3.5 percent over the FY 2003 amended President's Budget Request. A five year history of FTEs and Funding Levels for NCI are shown in the graphs below. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.





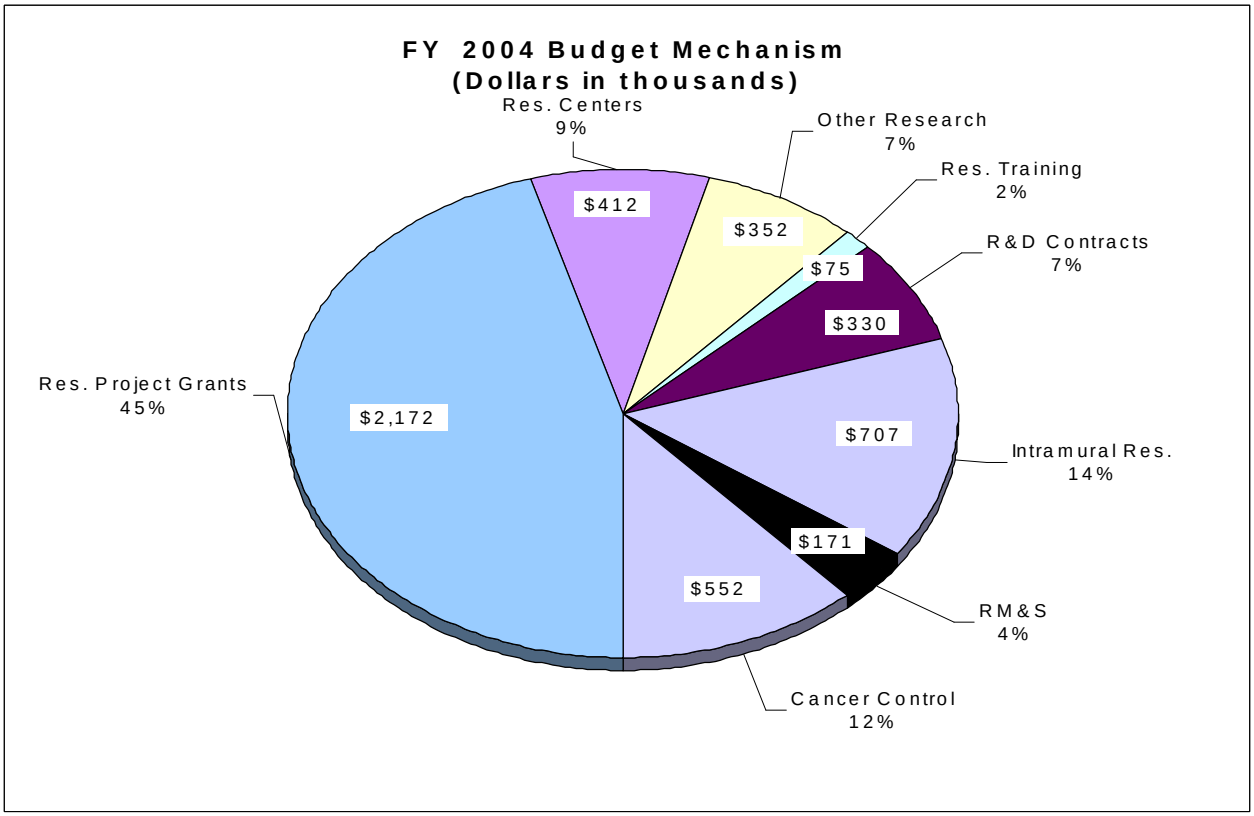
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. NCI will provide an aggregate average cost increase of 1.9 percent for Research Project Grants (RPGs).

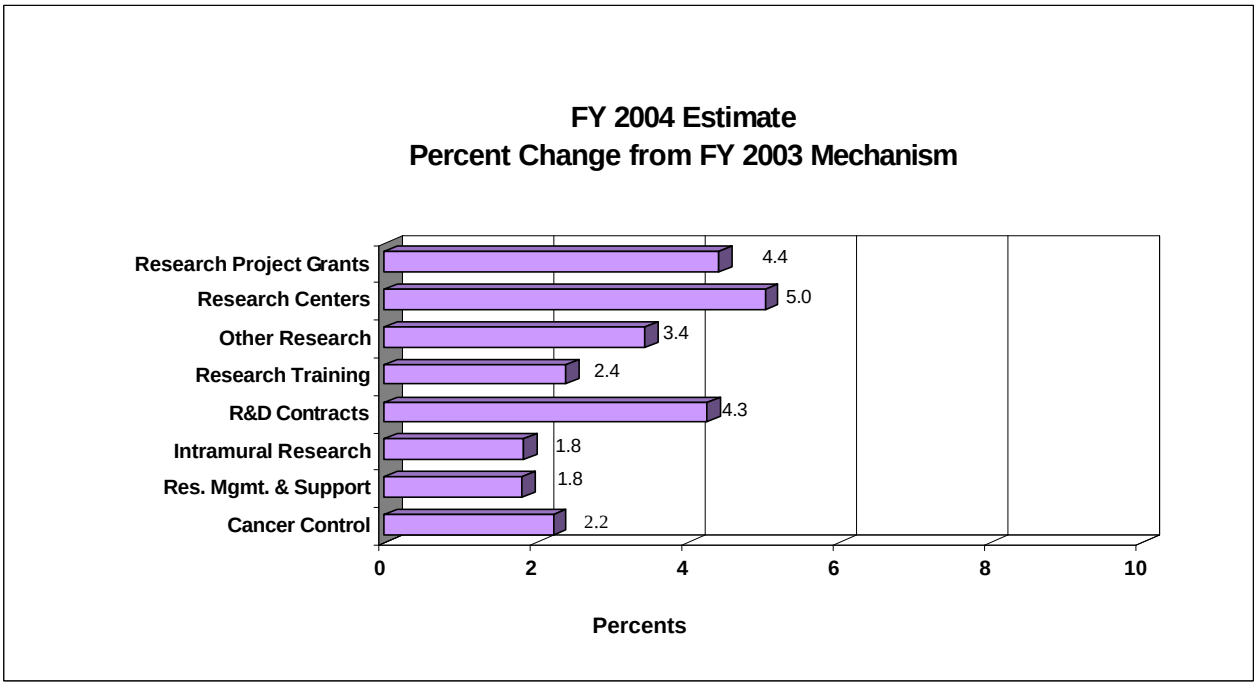
Also in FY 2004, NCI will fully fund 24 grants. These include Academic Research Enhancement Award (AREA) grants and Shannon Awards (R55).

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NCI will support 1,761 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2003. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2003 levels for predoctoral fellows, and from 4-1 percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 115 research centers, 917 other research grants, including 472 clinical career awards, and 236 R&D contracts. The R&D contract mechanism also includes support for the Best Pharmaceuticals for Children's Act. Intramural Research and Research Management and Support receive increases of 1.8 percent over FY 2003.

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





NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism - Total

MECHANISM	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,296	$1,307,020,000	3,434	$1,431,931,000	3,541	$1,506,176,000
Administrative supplements	(309)	46,659,000	(402)	56,744,000	(427)	55,244,000
Full funded	0	0	0	0	24	3,500,000
Single year	1,192	408,940,000	1,346	492,669,000	1,337	505,545,000
Renewal	317	156,819,000	366	176,131,000	361	174,148,000
New	854	248,622,000	968	312,738,000	970	328,322,000
Supplements	21	3,499,000	12	3,800,000	6	3,075,000
Subtotal, competing	1,192	408,940,000	1,346	492,669,000	1,361	509,045,000
Subtotal, RPGs	4,488	1,762,619,000	4,780	1,981,344,000	4,902	2,070,465,000
SBIR/STTR	370	85,528,000	350	98,410,000	360	101,210,000
Subtotal, RPGs	4,858	1,848,147,000	5,130	2,079,754,000	5,262	2,171,675,000
Research Centers:						
Specialized/comprehensive	107	319,753,000	113	392,308,000	115	412,058,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	107	319,753,000	113	392,308,000	115	412,058,000
Other Research:						
Research careers	420	54,867,000	456	64,577,000	472	66,827,000
Cancer education	96	26,775,000	101	29,206,000	105	30,206,000
Cooperative clinical research	137	163,826,000	143	174,330,000	148	180,330,000
Biomedical research support	0	6,133,000	0	6,500,000	0	6,700,000
Minority biomedical research support	0	3,980,000	0	4,522,000	0	4,672,000
Other	163	48,521,000	186	61,303,000	192	63,433,000
Subtotal, Other Research	816	304,102,000	886	340,438,000	917	352,168,000
Total Research Grants	5,781	2,472,002,000	6,129	2,812,500,000	6,294	2,935,901,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	131	5,219,000	204	8,545,000	204	8,750,000
Institutional awards	1,409	57,507,000	1,557	64,744,000	1,557	66,298,000
Total, Training	1,540	62,726,000	1,761	73,289,000	1,761	75,048,000
Research & development contracts	217	298,240,000	230	316,471,000	236	329,971,000
(SBIR/STTR)	(7)	(2,700,000)	(5)	(2,276,000)	(7)	(2,904,000)
	FTEs		FTEs		FTEs	
Intramural research	1,917	635,712,000	1,995	694,258,000	1,962	707,051,000
Research management and support	676	153,371,000	698	167,700,000	687	170,758,000
Cancer prevention & control	464	486,622,000	448	539,767,000	441	551,790,000
Construction		5,000,000		5,000,000		0
Total, NCI	3,057	4,113,673,000	3,141	4,608,985,000	3,090	4,770,519,000
(Clinical Trials)		(702,142,000)		(758,100,000)		(780,800,000)

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:								
Cancer causation	978	$1,074,289	987	$1,206,482	969	$1,238,167	(18)	$31,685
Detection and diagnosis research	186	267,215	187	312,546	184	336,516	(3)	23,970
Treatment research	936	1,094,521	943	1,199,201	928	1,229,342	(15)	30,141
Cancer biology	452	692,749	455	754,563	448	800,051	(7)	45,488
Subtotal, Research	2,552	3,128,774	2,572	3,472,792	2,529	3,604,076	(43)	131,284
Resource Development:								
Cancer centers support	20	323,817	20	396,619	20	414,784	0	18,165
Research manpower development	41	151,131	42	174,285	42	179,534	0	5,249
Construction	1	5,768	0	5,947	0	0	0	(5,947)
Subtotal, Resource Development	62	480,716	62	576,851	62	594,318	0	17,467
Cancer Control & Prevention	443	504,183	507	559,342	499	572,125	(8)	12,783
Total	3,057	4,113,673	3,141	4,608,985	3,090	4,770,519	(51)	161,534

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes

2003 Amended President's Budget				$4,608,985,000
2004 Estimated Budget Authority				4,770,519,000
Net change				161,534,000
	2003 Amended President's Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$231,975,000		$3,014,000
b. Annualization of January 2003 pay increase		231,975,000		1,805,000
c. January 2004 pay increase		231,975,000		3,493,000
d. One extra day of pay		231,975,000		889,000
e. Payment for centrally furnished services		121,463,000		2,429,000
f. Increased cost of laboratory supplies, materials, and other expenses		340,820,000		5,285,000
Subtotal				16,915,000
2. Research Management and Support:				
a. Within grade increase		69,927,000		1,132,000
b. Annualization of January 2003 pay increase		69,927,000		544,000
c. January 2004 pay increase		69,927,000		1,053,000
d. One extra day of pay		69,927,000		268,000
e. Payment for centrally furnished services		14,828,000		297,000
f. Increased cost of laboratory supplies, materials, and other expenses		82,945,000		1,286,000
Subtotal				4,580,000
3. Cancer prevention and control:				
a. Within grade increase		50,744,000		761,000
b. Annualization of January 2003 pay increase		50,744,000		395,000
c. January 2004 pay increase		50,744,000		764,000
d. One extra day of pay		50,744,000		194,000
e. Payment for centrally furnished services		4,564,000		91,000
f. Increased cost of laboratory supplies, materials, and other expenses		115,024,000		1,784,000
Subtotal				3,989,000
Subtotal, Built-in				25,484,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes--continued

CHANGES	2003 Amended President's Budget Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,434	$1,488,675,000	107	$72,745,000
b. Competing	1,346	492,669,000	15	16,376,000
c. SBIR/STTR	350	98,410,000	10	2,800,000
Total	5,130	2,079,754,000	132	91,921,000
2. Research centers	113	392,308,000	2	19,750,000
3. Other research	886	340,438,000	31	11,730,000
4. Research training	1,761	73,289,000	0	1,759,000
5. Research and development contracts	230	316,471,000	6	13,500,000
Subtotal, extramural				138,660,000
	FTEs		FTEs	
6. Intramural research	1,995	694,258,000	(33)	(4,122,000)
7. Research management and support	698	167,700,000	(11)	(1,522,000)
8. Cancer control and prevention	448	539,767,000	(7)	8,034,000
9. Construction		5,000,000		(5,000,000)
Subtotal, program		4,608,985,000		136,050,000
Total changes	3,141		(51)	161,534,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Object

	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	3,141	3,090	(51)
Full-time equivalent of overtime & holiday hours	12	12	0
Average ES salary	$142,001	$145,232	$3,231
Average GM/GS grade	11.4	11.4	0.0
Average GM/GS salary	$68,911	$70,479	$1,568
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$75,224	$77,556	$2,332
Average salary of ungraded positions	92,259	94,358	2,099
OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$153,176,000	$157,166,000	$3,990,000
11.3 Other than Full-Time Permanent	75,992,000	77,950,000	1,958,000
11.5 Other Personnel Compensation	9,385,000	9,628,000	243,000
11.7 Military Personnel	7,856,000	8,060,000	204,000
11.8 Special Personnel Services Payments	40,533,000	41,574,000	1,041,000
Total, Personnel Compensation	286,942,000	294,378,000	7,436,000
12.1 Civilian Personnel Benefits	60,499,000	62,067,000	1,568,000
12.2 Military Personnel Benefits	5,206,000	5,340,000	134,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**352,647,000**	**361,785,000**	**9,138,000**
21.0 Travel & Transportation of Persons	14,801,000	15,074,000	273,000
22.0 Transportation of Things	1,685,000	1,717,000	32,000
23.1 Rental Payments to GSA	3,000	3,000	0
23.2 Rental Payments to Others	2,296,000	2,338,000	42,000
23.3 Communications, Utilities & Miscellaneous Charges	8,068,000	8,219,000	151,000
24.0 Printing & Reproduction	4,193,000	4,281,000	88,000
25.1 Consulting Services	18,874,000	19,248,000	374,000
25.2 Other Services	197,850,000	198,530,000	680,000
25.3 Purchase of Goods & Services from Government Accounts	381,776,000	386,364,000	4,588,000
25.4 Operation & Maintenance of Facilities	114,599,000	117,490,000	2,891,000
25.5 Research & Development Contracts	331,773,000	346,458,000	14,685,000
25.6 Medical Care	3,367,000	3,428,000	61,000
25.7 Operation & Maintenance of Equipment	15,110,000	15,394,000	284,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**1,063,349,000**	**1,086,912,000**	**23,563,000**
26.0 Supplies & Materials	54,329,000	55,328,000	999,000
31.0 Equipment	32,098,000	32,686,000	588,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	3,075,497,000	3,202,157,000	126,660,000
42.0 Insurance Claims & Indemnities	4,000	4,000	0
43.0 Interest & Dividends	15,000	15,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**4,256,338,000**	**4,408,734,000**	**152,396,000**
Total Budget Authority by Object	**4,608,985,000**	**4,770,519,000**	**161,534,000**

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Salaries and Expenses

OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$153,176,000	$157,166,000	$3,990,000
Other Than Full-Time Permanent (11.3)	75,992,000	77,950,000	1,958,000
Other Personnel Compensation (11.5)	9,385,000	9,628,000	243,000
Military Personnel (11.7)	7,856,000	8,060,000	204,000
Special Personnel Services Payments (11.8)	40,533,000	41,574,000	1,041,000
Total Personnel Compensation (11.9)	**286,942,000**	**294,378,000**	**7,436,000**
Civilian Personnel Benefits (12.1)	60,499,000	62,067,000	1,568,000
Military Personnel Benefits (12.2)	5,206,000	5,340,000	134,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**352,647,000**	**361,785,000**	**9,138,000**
Travel (21.0)	14,801,000	15,074,000	273,000
Transportation of Things (22.0)	1,685,000	1,717,000	32,000
Rental Payments to Others (23.2)	2,296,000	2,338,000	42,000
Communications, Utilities and Miscellaneous Charges (23.3)	8,068,000	8,219,000	151,000
Printing and Reproduction (24.0)	4,193,000	4,281,000	88,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	17,692,000	18,034,000	342,000
Other Services (25.2)	197,850,000	198,530,000	680,000
Purchases from Govt. Accounts (25.3)	258,515,000	261,667,000	3,152,000
Operation & Maintenance of Facilities (25.4)	22,746,000	23,157,000	411,000
Operation & Maintenance of Equipment (25.7)	15,110,000	15,394,000	284,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**511,913,000**	**516,782,000**	**4,869,000**
Supplies and Materials (26.0)	52,675,000	53,643,000	968,000
Subtotal, Non-Pay Costs	595,631,000	602,054,000	6,423,000
Total, Administrative Costs	**948,278,000**	**963,839,000**	**15,561,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORT

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

Anti-cancer drugs -- The Committee is aware that the NCI is collaborating on the development of synthetic small molecule drugs that target both novel and known targets in cell cycle regulation. The Committee understands that these compounds leave normal, non-cancer cells unharmed while inducing cell-suicide in cancer cells. The Committee encourages the NCI to continue to fund this unique research effort. (p. 99)

Action taken or to be taken

The National Cancer Institute (NCI) supports the development of promising anti-cancer agents for human clinical trials through two mechanisms: 1) The Rapid Access to Intervention Development (RAID) is a competitive, peer reviewed program which provides assistance for the translation of novel anticancer therapeutic agents arising in the academic laboratory to human clinical trials. Approved applications to RAID gain access to the drug development contract resources of NCI. The output are provided to the originating investigator for support of an investigator-held IND application and clinical trials. 2) The Drug Development Group (DDG), comprised of NCI staff, approves early and late-stage development of agents proposed by researchers from endogenous NCI laboratories, academia, non-profit groups, and from the pharmaceutical industry. When the NCI collaborates with the pharmaceutical industry, its role is to increase the accessibility of patients to company-owned compounds by defraying the cost of research and regulatory requirements. This is a continuing example of public-private partnerships in the interest of advancing the public health. Successful applications receive NCI development contract resources and NCI-sponsored clinical trials. We continue to support these programs and actively encourage investigators to apply for support.

There are currently 22 RAID and DDG compounds that are either in preclinical development, in early state NCI-sponsored clinical trials; or have been returned to the academic investigator for them to pursue clinical trials or further development work.

RAID Compounds:

Methoxyamine: Novel biochemical inhibitor of the Base Excision Repair (BER) pathway. Synergizes with compounds whose DNA damage is normally repaired by BER, such as methylating agents. Confirmed synergistic cytotoxicity in tumor cell lines treated with both methoxyamine and temozolomide. RAID support: IND-directed toxicology and pharmacology, assay development, and acquisition of bulk substance, production of radio-labeled compound, as well as additional tumor model studies.

Thapsigargin: Specific inhibitor of the endoplasmic reticulum Ca 2+ -ATPase pump. Delivered in a prodrug form that is selectively activated at sites of metastatic prostate cancer by the serine protease activity of Prostate-Specific Antigen. This selective activation decreases the potential for systemic toxicity. RAID support: natural product recollection and purification, small scale (non-GMP) synthesis, and *in vivo* efficacy studies.

OMDPI: PI3 kinase is an important constituent of growth factor and oncogene signaling pathways. OMDPI is a potent inhibitor of this pathway and may be clinically useful in the treatment of a variety of neoplasms. RAID support: synthesis, *in vivo* testing, initial formulation development, and initial toxicology and pharmacology.

Immucillin-H: Treats T-cell proliferative disorders by specifically inducing apoptosis in populations of immature, transformed T-cells. Immucillin-H is a transition state inhibitor of purine nucleoside phosphorylase (PNP) which is 20,000 times more active against PNP than compounds currently in clinical trials against this target. RAID support: small scale synthesis, and *in vivo* efficacy studies.

erbB-2 Inhibitor: In cancers with erbB-2 over-expression, abnormal cell proliferation is caused by extremely high tyrosine kinase activity. ErbB-2 selective kinase inhibitor interrupts the signal transduction cascade mediated by erbB-2 and may have therapeutic potential for the treatment of cancers with erbB-2 over expression. RAID support: initial and IND-directed toxicology and pharmacology studies, early ADME profiling, *in vivo* based SAR of lead compound, and scale-up production for clinical trials.

Drug Development Group (DDG) Compounds:

*2-Methoxy Antimycin A1: Novel and potent inhibitor of Bcl-x_L's (anti-apoptotic protein) pore-forming activity; selectively kills cells over-expressing Bcl-x_L; active *in vivo* against human myeloma 8226 tumors. Currently undergoing animal testing and early phase pharmacology.

Zebularine: Acid-stable inhibitor of DNA methyltransferase that can provide a unique potential for oral dosing; potential to target and reactivate tumor suppressor genes; modest activity against murine B16 melanoma, P388 leukemia, and L1210 leukemia. Additional animal studies and pharmacology are underway.

Halofuginone: Novel antiangiogenic; potent inhibitor of collagen type I gene expression and MMP-2 activity; inhibits tumor stromal support, angiogenesis, invasiveness, and cell proliferation. Systemic formulation - *In vivo* activity against sarcoma; glioma; and bladder, breast, and prostate carcinomas. Topical formulation - Potential indications include Kaposi's sarcoma and other skin tumor models. Range-finding toxicology studies are planned.

BAY 43-9006: Raf kinase inhibitor; inhibits cell proliferation; evidence of anticancer activity in patients with solid tumors in Phase I trials.

Triapine: Ribonucleotide reductase inhibitor; approximately 1000-fold more potent than hydroxyurea; *in vivo* antitumor activity against murine L1210 leukemia, M109 lung carcinoma, B16F10 melanoma, and human HTB177 lung, DLD1 colon, and A2780 ovarian carcinoma; evidence of antitumor activity in a Phase I metastatic cancer trial.

Cordycepin/Deoxycoformycin: Potent cytotoxicity against TdT-positive cells. Currently in Phase I clinical trials.

UCN-01: PK inhibitor; *in vitro* activity against several cell lines; *in vivo* activity against A498 renal and MCF-7 breast. Several clinical trials underway.

Flavopiridol: CDK inhibitor with *in vitro* activity vs. lung, breast, and prostate. Several clinical trials underway.

COL-3: *In vitro* and *in vivo* activity as a tetracyclic inhibitor of matrix metalloproteinases, tumor invasion, and metastasis of a variety of tumor types. Currently in clinical trials.

Sugen 5416 (TK Inhibitor of VEGF- KDR): Inhibits VEGF-mediated signaling through Flk-1; inhibits endothelial cell proliferation *in vitro*; broad spectrum of antitumor activity in preclinical models. Phase I clinical trials underway.

R115777 (Farnesyl Transferase Inhibitor): Inhibits the growth of H-ras-, K-ras-, and N-ras-transformed tumors *in vitro* and *in vivo*. Phase I clinical trials in progress.

SU6668: Tyrosine kinase inhibitor (PDGFR, FGFR, VEGFR): Antiangiogenic and antiproliferative activity; *in vivo* activity against various human tumor xenograft models (melanoma; glioma; and lung, colon, ovarian, and epidermoid tumors). In Phase I clinical trials.

MS-275: Potent histone deacetylase inhibitor with novel chemical structure; *in vitro* and *in vivo* activity against a number of tumor cell lines. Several Phase I clinical trials underway.

BMS-275291: MMP inhibitor that spares sheddases; no dose-limiting arthritis has been reported in patients treated at doses up to 2,400 mg/day.

ZD1839 (Iressa): Potent and selective inhibitor of EGFR tyrosine kinase; active *in vivo* against a number of tumor xenograft models over expressing EGFR; demonstrated antitumor activity in patients with NSCLC.

STI571: Potent inhibitor of Abl tyrosine kinase both *in vitro* and *in vivo*; active in animal studies against CML and other Bcr-Abl-positive leukemias. Potential activity against tumors that express receptors for platelet-derived growth factor (PDGF) and stem-cell factor (SCF) (i.e., c-Kit). In Phase I clinical trials.

OSI-774: Selective epidermal growth factor tyrosine kinase inhibitor. *In vivo* antitumor activity against HN5 head and neck tumors and A431 epidermoid carcinoma. Agent well tolerated in Phase I clinical trials.

Item

[Risk determination and communication] -- The Committee is particularly supportive of work on risk determination and better communication of that risk to the public and public health infrastructures. The NCI is uniquely positioned to develop and expand large collaborative human population studies that can help build the science base. The NCI is also encouraged to expand research efforts to define the biological, behavioral, and social bases of tobacco use and addiction, and to refine treatment options for specific groups (e.g. pregnant women or young smokers). (p. 99)

Action taken or to be taken

Behavioral science provides a critical foundation for effective cancer prevention and control. Behavioral risk factors such as smoking, poor diet, and lack of exercise account for a large proportion of the national cancer burden. Similarly, most of the recent progress in reducing cancer morbidity and mortality has been a direct result of behavior change: the steady reduction of tobacco use among adults.

The National Cancer Institute (NCI) can and should be an international leader in behavioral science. This is vital not only to the mission of NCI, but also to the NIH's mission to accelerate the development and application of knowledge about health behavior and disease prevention. Many of the behaviors that increase one's risk of cancer also increase the risks of other chronic diseases, such as cardiovascular disease. Therefore, it is important for us to support both basic (fundamental mechanisms) and applied (cancer control-specific) behavioral science, just as we support both basic and applied biomedical science.

Five years ago, NCI had a small portfolio of behavioral research projects, largely focused on smoking, fruit and vegetable consumption, and mammography utilization. With the establishment of the Behavioral Research Program at NCI, we undertook a major effort to evaluate, strengthen, and expand both the breadth of the research program and the expertise of the scientists who lead it. In addition to the traditionally supported areas of research, we

expanded our support of interdisciplinary sciences in areas such as risk communication, decision-making, sociocultural research, consumer health informatics, policy analysis, neuroscience, and behavioral genetics.

In line with our mission, we make special efforts to coordinate our work with colleagues at the Centers for Disease Control and Prevention (CDC), the NIH Office of Behavioral and Social Sciences Research, and NIH institutes with major behavioral science programs. Within NCI, our role also includes championing the relevance of behavioral science to basic and clinical science programs across NCI. NCI's strengthened commitment to behavioral science research is evident by the designation of Cancer Communications, Tobacco and Tobacco-Related Cancers, Health Disparities, and most recently Cancer Survivorship as areas which are among the highest scientific priorities of the Institute. The Behavioral Research Program is leading numerous initiatives under these scientific priorities, with broad participation and support from the entire Institute. Examples of programmatic initiatives in these areas are described below.

Tobacco Control

Transdisciplinary Tobacco Use Research Centers. Seven Transdisciplinary Tobacco Use Research Centers (TTURCs) were established in 1999 with 5 years of funding by NCI, the National Institute on Drug Abuse, and the Robert Wood Johnson Foundation. These novel centers are designed to bridge disciplinary barriers; establish new conceptual frameworks and methods to understand and treat tobacco use; speed the transfer of innovative approaches to communities nationwide; and create a core of new tobacco control researchers. The centers establish critical links across diverse scientific disciplines. They are creating innovative research techniques and technologies that are providing new perspectives on tobacco use and addiction and are pioneering interventions to decrease tobacco use.

Youth Tobacco Research. Cutting-edge research is beginning to yield insights into nicotine addiction and dependence. Studies revealed, for example, that adolescent smokers can experience withdrawal within one month of smoking initiation. A recently published study showed that not all tobacco dependence in youth is physiological, but that psychological determinants of dependence are equally significant.

Women and Smoking. NCI, in partnership with the NIH and DHHS Offices of Women's Health, the American Cancer Society, and other invited agencies, will hold a conference focused on women, tobacco, and cancer. The goals are to identify gaps in research, recommend priorities, and identify effective ways to disseminate research findings and interventions that relate to decreasing tobacco use among women and girls.

Deliver Evidence-Based Interventions. In an effort to promote the adaptation and adoption of evidence-based interventions, NCI updated and adapted *Clear Horizons* and the *Guia para dejar de fumar* (Guide to Quitting Smoking) as part of a smoking cessation project targeted to Medicare beneficiaries in collaboration with the Centers for Medicare and Medicaid Services. Both products were developed by NCI-funded intervention research. *Clear Horizons* was developed at the Fox Chase Cancer Center in Philadelphia, Pennsylvania for English-speaking

adults aged 50+. The *Guia* was originally designed for and tested among a diverse Hispanic population in Northern California by the University of California at San Francisco. Key components of the *Guia* that were linked to quitting included graphic photographs of the physiological effects of tobacco use, a family-oriented health emphasis, and a format that was culturally appropriate for diverse Hispanic audiences. Approximately 10,000 copies of *Clear Horizons* and 95,000 copies of the *Guia* are being distributed.

Health Promotion of lifestyle factors that affect cancer risk

5 A Day Program/Health Promotion Activities. *5 A Day for Better Health* is one of the most widely recognized health promotion messages in the world. More than 35 countries have developed programs to increase fruit and vegetable consumption using the *5 A Day for Better Health* Program as a model. The program -- a noteworthy example of government agencies working together with private industry, voluntary health organizations, and advocacy groups -- is the largest public-private partnership for nutrition in the United States. **NCI will continue to build and nurture the *5 A Day for Better Health* program partnerships, and segment communication campaigns to deliver health messages to underserved populations.** The *5 A Day* campaign for African-American men plans to use blackhealthnetwork.com, *Black Enterprise* magazine, African-American civic organizations, and other targeted strategies to increase fruit and vegetable consumption. NCI will continue to develop and analyze the program, as well as other *5 A Day* campaigns, to determine how best to increase access to successful, evidence-based prevention messages. In addition, NCI will spearhead the newly developed partnership between the U.S. Department of Health and Human Services and the U.S. Department of Agriculture to further the *5 A Day* message in American schools.

NCI-Funded Evidence-Based Interventions. In a groundbreaking partnership, NCI has collaborated with the American Cancer Society (ACS) to adapt two successful NCI-funded intervention studies to create *Body & Soul: A Celebration of Healthy Living*, a nutrition program delivered through African-American churches. NCI and ACS also developed the Body & Soul program guide, which assists regional ACS offices in enrolling participants and conducting the program. Currently, the pilot program is operating in 15 churches (1,047 participants) in 3 ACS regions. The project has exceeded expectations for the feasibility of conducting intervention research in a real-world setting. The program is an example of effective research dissemination to communities, as well as successful research collaboration between NCI and ACS.

Cancer Communications

Centers of Excellence in Cancer Communications. These Centers will facilitate rapid advances in knowledge about cancer communications and develop, implement, and evaluate strategies to improve access to and the efficacy, effectiveness, and dissemination of cancer communications. By assembling interdisciplinary teams of researchers committed to answering important health communications questions, and by ensuring adequate infrastructures, we can speed the process of discovery to delivery. These NCI-funded centers will focus on the advancement of cancer communication science across the cancer continuum. Their interdisciplinary efforts should result in new and/or improved syntheses, theories, methods, and interventions.

Health Information National Trends Survey (HINTS). HINTS, the first national health communications survey, will collect nationally representative data every two years from 8,000 randomly selected adults about the public's need for, access to, and use of cancer-related information. Examples of survey topics include information seeking about cancer, knowledge about cancer, attitudes and beliefs about cancer screening, and cancer-related health risk behaviors. The data gathered through the HINTS will yield data on perceptions of cancer risks, identify and examine preferred information channels, and determine the cancer-related health information needs of the public. We specifically are assessing peoples' reactions to 9/11 in terms of health behaviors. Over the past year, NCI has obtained extensive input on the survey contents from a variety of experts. The first survey will be fielded in late 2002. Data analysis will take place immediately after, with preliminary data available within two months. NCI staff are developing protocols to assure that the scientific community has rapid access to the data, and that some reports are created especially for lay persons.

Making Quality Count for Consumers and Patients. In general, research has found that people have trouble understanding risk information that involves quantitative data and probabilities. As part of an NCI/Agency for Healthcare Research and Quality initiative, an NCI-funded grant was awarded to researchers at Dartmouth College to develop and evaluate a primer to help people use numbers in health, as well as three basic risk communication tools to supplement the primer: cancer risk charts, prevention benefit charts, and standard disease summary templates. The researchers are revising the primer based on qualitative interviews and have completed a pilot study of the new survey measures they developed for testing the primer. Findings from this study can help us frame risk information appropriately to different audiences and provide a model for how to present quantitative risk data. This is directly applicable to communicating about agents like anthrax and to recommend specific actions often with uncertain evidence.

Decision Aids. A new 5-year grant that was funded in April 2002 aims to identify and reduce cognitive biases created by decision aids. Decision aids inform patients about the probability of various harms and benefits associated with available treatment alternatives. They have great potential to help patients make informed decisions, with application that extends beyond cancer.

Health Disparities

Centers for Population Health and Cancer. Research has rapidly increased our understanding of the complex biological and behavioral factors that lead to cancer. Yet it is clear that, in order to make further progress, we must build on this impressive record of fundamental discovery and expand our understanding of the broader social determinants of cancer. Social determinants, which include environmental, cultural, and social factors, influence exposure and vulnerability to disease, behaviors that increase risk of cancer, the effectiveness of health promotion efforts, and the likelihood of diagnosis in the late stage of disease. These factors also impact access to and the quality of health care delivered to cancer patients. They play a role in the disparities in cancer outcomes between groups defined by racial, ethnic, and socioeconomic status. The new Centers for Population Health and Health Disparities will provide the interdisciplinary research approach needed to reduce the unequal burden of cancer and help achieve the goal of making cancer an uncommon disease that is easily treated. In Fiscal Year 2003, the centers will

accelerate knowledge about the causes of health disparities and develop effective interventions to reduce them.

Item

[Tumor Cells] -- The Institute is also encouraged to focus on understanding the interaction between tumor cells and a multitude of cells in the bone microenvironment, as well as the role of extra cellular matrix and a multitude of growth factors, cytokines and other proteins on tumor survival and growth in the bone. (p. 99)

Action taken or to be taken

Most people die not because of the tumor in the primary site but rather as a result of the tumor having spread to other sites. Although it is difficult to determine how frequently tumors metastasize to the bone, it is known that a high percentage of patients with prostate cancer, breast cancer and multiple myeloma develop bone metastasis. Bone metastases are also frequently seen in patients with lung cancer, renal cancer and melanoma. There are approximately 350,000 deaths per year in the US from cancer patients with bone metastasis.

Bone metastases are associated with frequent intractable bone pain, bone fragility and deformity, bone fractures, hypercalcemia, nerve compression syndromes such as spinal cord depression, and death. There are two types of bone metastasis, osteolytic and osteoblastic. In osteolytic lesions, factors such as parathyroid related protein and interleukins are released by tumor cells in the bone microenvironment. These factors act on bone cells, which in turn, produce factors that stimulate osteolytic (bone resorption) or osteoblastic (new bone formation) activities. It is also evident that reciprocal interaction between tumor cells and the bone marrow microenvironment is critical in tumor cell survival and growth which eventually leads to the formation of bone metastasis. Both osteoblastic and osteolytic lesions are seen in patients with bone metastasis.

The relationship between prostate cancer and bone metastasis is unique among cancers. Approximately 90% of the advanced prostate cancer patients develop bone metastasis. One third of the patients with prostate specific antigen (PSA) greater than 20 at the time of diagnosis have radiologic evidence of bone metastasis. In addition, bone marrow samples of patients thought to have localized disease have frequently been shown to have PSA at the time of prostatectomy, suggesting that bone marrow metastasis may be an early event, even prior to clinical symptoms and nuclear radiographic positivity. Similarly, of the more than 44,000 deaths due to breast cancer in the U.S. in 2002, more than 80% of the breast cancer patients showed evidence of bone metastasis.

Multiple myeloma (MM), which represents 13% of all lymphoid cancers in the white population and 31% in the black population, is a severely debilitating as well as incurable cancer. The major source of morbidity and mortality associated with MM are osteolytic lesions that occur only in the area adjacent to the myeloma cells. New bone formation that normally occurs at the sites of bone destruction is also absent. These results suggest that locally active factors produced by myeloma cells induce extensive bone destruction and block new bone formation.

In order to improve therapy and ultimately prevent bone metastasis, 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 with the hope that the resulting information will help (a) to improve clinical trials using bisphosphonates, and (b) to stimulate basic research which will lead to a precise understanding of the pathophysiology of bone metastasis.

A very important example of therapies that target bone is the class of agents known as bisphosphonates, which are known to slow the progression of osteoporosis in women. Bisphosphonates are analogs of endogenous pyrophosphates in our bodies and are potent inhibitors of bone resorption. They significantly reduce morbidity due to bone metastasis in patients with advanced breast and prostate cancer as well as multiple myeloma. They have also been shown to reduce metastasis to the bone by human breast cancer cells in experimental models. Newer, more potent derivatives of bisphosphonates, the aminobisphosphates are currently in clinical trials. Although bisphosphonates significantly reduce skeletal morbidity associated with solid tumor metastasis to the bone, most studies indicate minimal improvement in survival. Another inhibitor of bone resorption, the protein osteoprotegerin, is also effective in animal models of breast and prostate cancer, and in reducing bone pain in patients.

A large nation-wide NCI trial has been launched to follow up and confirm promising initial data reported by investigators at the MD Anderson Cancer Center. In a preliminary clinical study published in 2001, patients receiving chemotherapy for advanced, androgen-independent prostate cancer with evident bone metastases were randomized to receive, in addition, Strontium-89, a radionuclide that is taken up by the bone in a very specific way. Not only did the patients exhibit a better PSA response as well as a dramatic reduction in bone pain, there was also what appeared to be an impressive prolongation of survival. It is hypothesized that this combined approach may be considerably more effective in suppressing the growth of neoplastic cells within the bone microenvironment, and since osteoblastic bone lesions represent by far the most predominant clinical manifestation of advanced prostate cancer, this approach may prove particularly promising.

The NCI was able to take advantage of its very large network of clinical investigators in the Cooperative Group system to rapidly set up a much larger scale definitive test of the approach piloted at MD Anderson. This study is now accruing patients who have been referred by qualified clinicians in the country under the aegis of the NCI's new Clinical Trials Support Unit mechanism. If the preliminary data are confirmed, this will represent an important proof-of-principle that the bone microenvironment is the special 'soil' in which some types of cancer readily establish and grow to form metastatic colonies. Since there are other classes of therapeutic agents that are able to target bone as well, but through different mechanisms, this is expected to be a productive line of research.

The current understanding of the molecular underpinnings of bone metastasis is very limited. However, several recent developments suggest that bone metastasis is a research area of great opportunities: 1) the availability of a number of experimental models, obtained by intracardiac or orthotopic injections, to study bone metastasis in prostate and breast cancer and in multiple

myeloma. In addition, implantation of human bone in SCID mice allows successful homing of prostate cancer and multiple myeloma cells specifically to the human bone. 2) The availability of microarray and related technologies and the laser capture micro-dissection technology permit evaluation of complex interactions, such as those involved in tumor-bone microenvironment interactions. 3) Significant advances in basic bone biology research, with development of a repertoire of critical reagents, have provided a large cohort of basic biologists who could enter the field of bone metastasis.

The NCI issued an initiative in May 2002, entitled “Molecular Interactions between Tumor Cells and Bone." The purpose of this Request for Application is to solicit grant applications from researchers interested in understanding the pathophysiology of bone metastasis, especially as it relates to tumor cell-bone stroma interactions. This will lead to a better understanding of the unique features of the bone and its microenvironment that renders it an attractive site for tumor cells. This multi-institutional initiative, co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), is expected to fund grant applications in FY 2003.

The identification of the molecular interactions between tumor and bone cells has progressed to the next stage where gene array technology may be applied to identify new targets for therapy. Tumor growth does not appear to be a major point of regulation of bone metastases, although growth is the most common parameter assayed in vitro. Applicants are therefore encouraged to use microarray and proteomics technologies to compare metastatic versus non-metastatic cells and design an efficient system for validating the physiological significance of identified candidate genes/proteins in vivo using animal models. Further, the role played by malignant tumor cells (e.g., breast and prostate cancer) on bone turnover also needs to be delineated.

Overall, research proposed under this initiative would help in elucidating 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. This would pave the way for optimal methods for the prevention and treatment of bone disease, since elucidating the basic mechanisms that drive this intricate process would allow potential points of intervention to be identified.

The NCI has identified the study of cancer microenvironment as an area of Extraordinary Opportunity in the 2004 Bypass Budget proposal. The main focus under this theme is to 1) define the molecular signatures of cells in the cancer microenvironment at various points during initiation and progression of cancer; 2) identify factors used by cancer cells to activate cells in the tumor microenvironment, which in turn support tumor growth and progression; 3) identify the origin of cells and factors that comprise the tumor microenvironment; 4) establish a repository for antibodies, cell lines, animal models, and tissues that relate to cells in the microenvironment; and 5) apply knowledge derived from molecular analysis studies exploring tumor-host interactions to create targeted interventions. Research under this Extraordinary Opportunity will also address issues related to bone metastasis observed in several human malignancies including, prostate and breast cancer and multiple myeloma.

The NCI has initiated or is participating in a number of Trans-NIH wide initiatives to address research issues that are relevant to tumor metastasis, including bone, and to cover a number of human cancers such as those of the prostate, breast, multiple lung and myeloma.

- A special Program Announcement "*Molecular and Cellular Biology of Metastatic Tumor Cells*" encourages investigators to submit novel applications in the area of tumor metastasis.
- Another Program Announcement, "*Bone Anabolic Hormones, their Receptors and Signal Transduction Studies*," solicits applications that focus on systemic hormones, local growth factors and bone-active cytokines with potential bone anabolic effects. Although the primary focus is on basic research, the long-term objective is to identify potential targets of therapeutic value in the treatment of tumor metastasis to bone.
- NCI is participating in a Program Announcement, entitled "Complex Formation in Hormonal Regulation of Gene Expression," that is designed to exploit and expand upon advances made in the area of hormonal regulation of gene expression, especially the role of novel factor(s) associated with steroid hormones in breast and prostate cancer. An area of great interest in cancer biology is that bone metastases in these tumors often progress to a stage where they are estrogen- or androgen-independent.
- NCI is also initiating a new Program Announcement, "*High Impact Pilot Studies in Cancer Biology*," that will encourage opportunities to support research in new areas that may lead to novel insights in the understanding and combating of the cancer process.

Since 2000, the NCI has organized or co-sponsored several workshops or international symposia related to tumor microenvironment with special emphasis on bone metastasis. In November 2000, NCI organized a workshop entitled "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities," that 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 the following areas: 1) understanding the unique features of the bone and its microenvironment that render it an attractive site for tumor cells; 2) ideal experimental models that were useful in studying bone metastasis; and 3) possible targets in the bone that could be used in directing therapy once metastasis has occurred.

In April 2002, NCI co-sponsored the "Third North American Symposium on Skeletal Complications of Malignancy." This 3-day symposium focused on (a) bone marrow microenvironment and animal models of bone metastasis, (b) biology and clinical aspects of bone metastasis in prostate cancer, (c) biology and clinical aspects of bone metastasis in breast cancer, (d) biology and clinical aspects of bone metastasis in multiple myeloma, (e) preclinical and clinical studies on bone metastasis: future directions, and (f) current and future status of adjuvant therapy of bone metastasis. NCI will be co-sponsoring the "Fourth International Conference on Cancer-Induced Bone Diseases," in San Antonio in December 2003. The conference will provide clinicians and basic researchers, including biologists, urologists, oncologists and endocrinologists, with a comprehensive program on the most recent advances made in the pathophysiology and management of patients with cancers. Discussions will involve

the skeleton and specific cancers with possibility for bone metastases, including breast and prostate cancers, and multiple myeloma.

The NCI is part of two federal working groups. The first, the "Federal Working Group on Bone Diseases," has members from many institutes at the NIH as well as representation from other federal agencies. The second more recently established Federal Working Group is focused on promoting research in the area of lymphatics, and has members representing various institutes of the NIH as well as members from the Lymphatic Research Association. Lymphangiogenesis, or the formation of new lymph vessels, is important in the dissemination of tumor cells to different sites, especially in solid tumors. Since many solid tumors, including breast, prostate, lung, renal and melanoma, metastasize to bone, research in lymphangiogenesis will help to better understand the process of tumor metastasis, including bone metastasis. NCI will sponsor a 3-day workshop on Lymphangiogenesis and Cancer Metastasis in 2003. This workshop will assemble a multidisciplinary group of investigators including cancer biologists, clinical oncologists, and vascular biologists and imaging experts to address the issues of tumor lymphangiogenesis biology, markers of lymphangiogenesis, its regulation and its potential as a therapeutic target.

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 of metastatic tumor cells in a manner that changes tumor behavior. Furthermore, some of the molecular mechanisms responsible for the bi-directional interaction between bone and tumor cells in vivo have been recently identified. A few examples are briefly described.

- 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.

- An osteoclast differentiation factor referred to as RANKL has been identified as a prerequisite for the formation and maintenance of osteoclasts from precursors. The study has also identified PTHrP as the protein responsible for activating RANKL, thereby creating a bone microenvironment conducive to the survival of PTHrP-producing cancer cells.

- Recent studies have identified another protein, interleukin-8, as a key determinant of breast cancer metastasis to the bone.

- Studies have shown that the protein endothelin –1 (ET-1) in breast cancer has many functions in the bone. While ET-1 promotes bone formation and tumor progression of breast cancer, it also retards bone resorption. 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.

- Matrix metalloproteinases (MMPs) are enzymes that play a crucial role in helping the tumor cells escape the confines of its organ of its origin by degrading the surrounding basement membrane. Hence MMPs are attractive therapeutic targets. Using experimental models of bone metastasis in breast and prostate cancer, synthetic MMP inhibitors are able to inhibit bone destruction as well as extend survival of mice with bone metastasis.

- Integrins are cell adhesion molecules that play a key role in several physiological processes, including development, organ formation, angiogenesis and tumor dissemination. The role of this protein is especially important in bone metastasis because of its role in several important processes, including bone resorption and tumor-associated angiogenesis. Recent work has shown that mice devoid of this protein are unable to form osteolytic bone metastasis when such animals are injected with human breast cancer or melanoma cells. This is an exciting finding that indicates that altering the tumor microenvironment may be an effective strategy in blocking bone metastasis of tumors.

- As stated earlier, bisphosphonates (BP) are specific inhibitors of osteoclastic bone resorption and are widely used therapeutic agents for bone metastases in breast cancer patients. To determine the effects of BP on visceral metastases, NCI-funded investigators administered BP in mice which have metastases in bone, lung and adrenal glands. Their results have conclusively shown that BP administration at the therapeutic dose has no adverse effects on visceral metastases in a breast cancer model.

- 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.

- A unique protein produced by 70% of myeloma cells is MIP-1 alpha, which has profound deleterious effects, including increased bone destruction and increased 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.

- 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 or inhibiting the strong interactions between tumor cells and bone stromal cells will not only be able to 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.

- 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 roles of several different types of proteins, including growth factors, proteases and adhesive proteins, have recently been recognized. This data suggests 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.

The NCI also 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 models should enable mechanisms to be elucidated and contribute background information for the design of further clinical trials.

The NCI supports new initiatives in drug development, based on the progress made over the last decade in the 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.

Item

Brain Tumor Progress Review Group -- The Committee is concerned that the NCI and NINDS have not proceeded with implementation of the Brain Tumor Progress Review Group's recommendations on advancing brain tumor research. The Committee strongly urges the NCI and NINDS to finalize their plan for implementing the recommendations and to provide additional funding for the NCI-NINDS Neuro-Oncology Program to ensure that the Federal research agency is a leader in brain tumor research. The two Institutes should also seek to expand their collaborative brain tumor research ventures, including interactive meetings involving scientists of different disciplines and interdisciplinary grant applications in brain tumor biology and etiology. The Committee requests that the NCI and NINDS report on their collaborative brain tumor research initiatives by December 31, 2003. (p. 99)

Action taken or to be taken

The National Cancer Institute (NCI) and the National Institute of Neurological Disorders and Stroke (NINDS) formed the Brain Tumor Progress Review Group (PRG) to assess the state of the science for this disease site and make recommendations for future research. The PRG reported the findings for this review in November 2000. The report of the PRG is available at (http://prg.nci.nih.gov/brain/finalreport.html). This report identified priority areas for future research. During its deliberations, the PRG provided numerous recommendations that fell into three major priority groups: crosscutting priorities, which foster additional communication

among scientists, clinicians and advocates involved in brain tumor research; research priorities for basic science and clinical research; and resource priorities, which help to provide tools required to advance the study of brain tumors.

In order to respond to the recommendations of the PRG, NCI and NINDS established a joint working group to identify ongoing and new activities relevant to the PRG recommendations, and to propose new strategies to help address remaining research gaps. In October 2002, NCI and NINDS released a summary of the results of this working group, the "Strategic Plan to Address the Recommendations of the Brain Tumor Progress Review Group" (http://prg.nci.nih.gov/brain/btumorprogress.pdf). The Strategic Plan outlines the approach that NCI and NINDS will use to implement the PRG recommendations, and both Institutes are promoting this document within the brain tumor advocacy and research communities. In addition, both Institutes are developing performance plans for each of the proposed new strategies in the Strategic Plan. NCI and NINDS will use these performance plans to facilitate and monitor implementation of the strategies. In 3 years, NCI and NINDS will issue a progress report that will summarize their progress in implementing the PRG recommendations. To inform the process of formulating new strategies, both Institutes conducted a comprehensive review of ongoing and new activities relevant to the PRG recommendations. Each of these activities is described in detail in the Strategic Plan; however, current (ongoing and new) activities are highlighted below.

NCI and NINDS are supporting a number of activities to foster interdisciplinary research. These jointly sponsored initiatives will help bring different groups of researchers together to address brain tumors, since NCI activities attract cancer researchers while NINDS initiatives typically focus on neuroscientists.

For example, some initiatives support interdisciplinary scientific meetings in brain tumor research, such as the Neuro-Oncology Models Forum and the Workshop on Gene-Environmental Interactions in the Etiology of Childhood Cancer. The workshop on gene-environmental interactions recently convened a multidisciplinary group of approximately 100 speakers and participants from academia and several governmental agencies. A summary of the meeting, which focused on lifestyle factors (e.g. nutrition, smoking, physical activity), chemical exposures, and the influence of infectious disease, will be published in the near future.

A second group of activities is building infrastructure to facilitate future collaborations, including the Cancer Genetics Network and the Shared Pathology Informatics Network. In addition, NCI and NINDS co-funded two Specialized Programs of Research Excellence (SPORE) in FY 2002. These programs support interdisciplinary teams of investigators to conduct translational research on brain tumors. A core mission of these SPOREs is to promote collaboration between laboratory scientists (including neuroscientists) and clinicians. One brain tumor SPORE is intended to create novel tools and therapies potentially useful in the treatment of human brain tumors. A second brain tumor SPORE is conducting studies on pathogenesis, anti-invasion strategies, glioma-host interactions, viral and gene therapy, and anti-angiogenesis therapy. NCI and NINDS plan to co-fund two additional brain tumor SPORES in FY 2004.

A third group of activities is encouraging the development of imaging techniques, which require incorporation of scientific expertise outside the traditional scope of biomedicine. Initiatives such as the Development and Application of Imaging in Therapeutic Studies, the Development of Clinical Imaging Drugs and Enhancers, the Development of Novel Imaging Technologies, Exploratory/Developmental Grants for Diagnostic Cancer Imaging, Cerebral Radiobiology and Neuroimaging of Brain Tumors and In Vivo Cellular and Molecular Imaging Centers are all advancing these powerful tools in brain tumor research.

The intramural NCI-NINDS Neuro-Oncology Branch (NOB) is working to develop treatments for tumors of the brain and spinal cord. A primary focus of the NOB is to create methods that selectively deliver therapies to the site of a brain tumor. Recent work at the NOB suggests that certain bone-marrow-derived neural stem cells can be used as efficient gene therapy vectors, because these cells can migrate to sites of brain tumor cell infiltration and to sites of neural tissue damage. Other NOB researchers are working on targeted gene therapy techniques, and new methods to deliver agents specifically to the angiogenic vasculature of growing tumors.

Additional NOB initiatives include a large-scale analysis of glioma gene expression patterns to improve tumor classification, patient prognosis, and the selection of therapies. The NOB has also established an animal brain tumor experimental therapeutics and diagnostic core to develop new brain tumor biomarkers using techniques such as imaging, gene expression analysis and the evaluation of proteomic patterns. The brain tumor experimental therapeutics and diagnostic core will also address some of specific challenges involved in pre-clinical development of brain tumor therapies, including the need for new agents that effectively traverse the blood-brain barrier.

In addition to extensive ongoing laboratory research at the NOB, the program is building substantial administrative and clinical infrastructure to treat brain tumor patients at NIH. These resources will facilitate the rapid dissemination of promising new therapies to brain tumor patients in new phase I and phase II clinical trials.

After completing an analysis of current activities relevant to the PRG recommendations, the NCI-NINDS joint working group convened to propose new strategies that address remaining gaps in the brain tumor research portfolio. The working group divided these strategies into four groups to reflect differences in the likely speed of implementation and degree of partnership required. Immediate strategies are currently being implemented. However, the speed of implementation will depend upon the availability of NCI staff to devote appropriate resources to the effort. Short-term strategies are under development. The ability to implement these strategies is dependent on a final evaluation of importance and feasibility, the availability of funds, and the receipt of high-quality applications. Medium-term strategies await future approval for further development by NCI and NINDS. Additional consideration of these strategies will take place over the next several months. Long-term strategies are those the two Institutes will not be able to pursue at this time. Implementation of all these strategies will require extensive partnering with external organizations.

Several of the working group's proposed new strategies address specific concerns identified by the Committee. Two short-term strategies jointly promoted by NCI and NINDS would provide

additional support for the intramural NCI-NINDS Neuro-Oncology Branch. These strategies include: 1) Providing additional support for the Glioma Molecular Diagnostic Initiative, a prospective, publicly available database containing data (including corollary clinical data) from molecularly characterized glioma specimens for the purpose of establishing a useful molecular classification scheme for gliomas. 2) Expanding the Cancer Molecular Analysis Program (CMAP), which will enable researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. A website will provide access to molecular phenotypes that best fit a query and will offer information about clinical trials of molecularly targeted agents specific to the phenotypes. NCI and NINDS will prototype this effort using data gleaned from the Glioma Molecular Diagnostic Initiative.

Three immediate strategies jointly promoted by NCI and NINDS would support interactive meetings of scientists from different disciplines. These include: 1) Fostering opportunities for development of interdisciplinary collaboration by integrating NINDS-supported neuroscientists into meetings and workshops of relevant crosscutting NCI initiatives such as the Director's Challenge Consortia, Brain Tumor SPOREs, and Brain Tumor Consortia. Similar reciprocal arrangements will be made for NCI-funded oncologists to participate in workshops and symposia related to key NINDS neuroscience initiatives. 2) Inviting Center for Scientific Review (CSR) staff to join a working group that will examine study sections' composition, behavior, and referral patterns for Brain Tumor-related grant applications to determine whether equal and broad expertise exists in the areas of both neuroscience and oncology. The possibility of initiating an exchange program within neuroscience and oncology study sections to ensure fair review of applications will also be discussed. 3) Establishing a brain tumor working group composed of NCI and NINDS staff, as well as CSR staff, that will, three times each year, review and report on each funding cycle's grant applications and review procedures, monitor outcomes, and identify gaps and problems that arise in implementing the PRG's recommendations.

Finally, NCI and NINDS have identified several short-term strategies to encourage interdisciplinary grant applications. These include: 1) Issuing a joint program announcement to encourage the application of new concepts in developmental neurosciences to understanding the unique organ-specific mechanisms of glioma biology in both pediatric and adult patients. These concepts include understanding stem and precursor cell biology and cell dispersal, differentiation, and signal transduction pathways as they relate to tumor cells within the central nervous system. This program announcement is currently in the planning stage. 2) Issuing a joint program announcement on Neuroprotective Barriers in Neurological Disease to support research aimed at understanding how neuroprotective barriers function and are compromised under disease conditions. Topics of interest include blood-brain barrier regulation, transport biology, and potential targeted drug delivery strategies. This announcement has recently been approved by both Institutes, and is currently under development. 3) Reviewing existing training programs to identify interdisciplinary research needs that could be addressed on a more targeted basis. Of relevance to this strategy, NINDS has recently funded an Institutional Training Program at the Mayo Clinic in Minnesota that is focused on interdisciplinary brain tumor research.

Item

Cancer and minorities -- The Committee remains concerned that cancer rates for Native Hawaiians and other Native American Pacific Islanders are disproportionately high. The Committee encourages the NCI to expand its research in this area. (p. 100)

Action taken or to be taken

The unequal burden of cancer in our society is more than a scientific and medical challenge. Certain populations experience the negative consequences of significant disparities in cancer incidence, the care they receive, and the outcomes of their disease. These differences have been recognized for some time but are now being documented with increasing frequency and clarity.

In August 2002, the NCI Director visited the University of Hawaii at Manoa and the Cancer Research Center of Hawaii. The Director had the opportunity to meet local oncologists and to hear the challenges Native Hawaiians and Pacific Islanders are facing regarding culturally competent and cutting-edge cancer care. The Director also visited Papa Ola Lokahi, a not-for-profit charitable consortium organization which serves as an umbrella for Native Hawaiian health care planning activities in the state. The Director valued the opportunity to hear about cancer concerns and advancements of Native Hawaiian and Pacific Islanders directly, and to confirm NCI's commitment to supporting the health and well-being of Native American populations.

Community Outreach

NCI sponsors 18 **Special Populations Networks for Cancer Awareness Research and Training** (SPNs) that build relationships with community-based programs, foster cancer awareness activities, increase minority enrollment in clinical trials, support pilot projects that will lead to the development of grant applications for new and innovative research, and develop junior biomedical researchers from minority and underserved communities. Collaborations with clinical/academic partnerships established between Network awardees and Cancer Centers, academic institutions, and Clinical Cooperative Groups are essential to all of these activities.

The 'Imi Hale Native Hawaiian Cancer Awareness Research and Training Network located in Honolulu recently completed its third 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, four pilot projects were competitively awarded for additional funding of $200,000. These projects include:

- Developing a program to decrease tobacco use.
- Exploring the feasibility of a family ('Ohana) intervention to promote the well-being of families of Native Hawaiian women with breast cancer.

- Exploring the feasibility of Ho'oponopono for enhancing adjustment & adaptation to breast cancer diagnosis & treatment among Native Hawaiians.
- Piloting a culturally appropriate intervention to increase colorectal cancer screening among Naive Hawaiians.

The September 2001 issue of the *Pacific Health Dialog - Journal of Community Health and Clinical Medicine for the Pacific* was dedicated to "The Health of the Hawaiians." This volume contains a number of articles by the ‘Imi Hale staff and their steering committee, including a focus on changes in breast cancer knowledge, attitudes and behavior and practices in Native Hawaiian women as well as establishing an inheritance for Native Hawaiians on cancer awareness, research and training.

Efforts are also underway to collaborate with ‘Imi Hale to perform initial assessments of the cancer concerns of the six regions of the Pacific Rim. Funds have been provided to begin these needs assessments that may indicate the nature of future activities in these regions.

Cancer Control

The Social and Behavioral Sciences Program at the Cancer Research Center of Hawaii (CRCH), a dedicated research unit of the University of Hawaii, was formally established in July of 2001. The Social and Behavioral Sciences Program (SBSP) unites a multidisciplinary team of investigators and staff to conduct innovative, socially relevant research to prevent and control cancer and other major chronic diseases. The NCI, along with the National Human Genome Research Institute (NHGRI), the Centers for Disease Control and Prevention (CDC), and state agencies including the Hawaii Department of Health (Alcohol and Drug Abuse Division) and the Office of Youth Services, serve as key funding organizations for the SBSP.

The emphasis of research at SBSP is on modifiable risk behaviors, early detection, social and health policy, and the use of new health communication technologies for disease prevention. General research interests lie in advancing the understanding of individual and communities' behaviors for cancer prevention and control, and in developing, implementing, and evaluating interventions to reduce cancer incidence, morbidity, and mortality. These interests have led to a research program based on five interrelated themes:

- Cancer prevention and detection among children, youth, and families;
- An emphasis on persons at high-risk for cancer and risk communication strategies to reach these persons;
- Ethnic factors, especially in Hawaii's diverse cultural groups;
- Social policy relevant to cancer prevention and control; and
- Use of innovative communication technologies to build healthy individuals, families, and communities.

These research themes are being applied to cancer prevention and control in the areas of sun protection and avoidance, tobacco control, healthy nutrition, colorectal cancer screening andgenetic testing, and limiting alcohol consumption. The program emphasizes community-

based research that involves strong collaborative relationships with individuals and groups in Hawaii and elsewhere. A hallmark of this research is its multi-sectoral collaborations with education, health care, public health, law enforcement, and social service agencies. Community research extends to all regions of the state of Hawaii, and all current studies in the state include both Oahu and Neighbor Island participants and agency partners.

As part of an NCI funded training program for Native American researchers in cancer control, several research projects have been supported. In FY 2002, three projects are providing preliminary results in Native Hawaiian and Asian Pacific communities.

- ***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 doctoral program. The research is defining the experience of both spirituality and cultural identity among Native Hawaiian cancer survivors.

- ***Validating A Measure of Religiousness/Spirituality for Native Hawaiians.*** Breast cancer survivors and family members who joined focus groups emphasized the importance of family support to deal with the illness and designation of one family member to act as liaison with the health care system. Participants indicated that an important source of stress for patients were family members who did not understand the scope or impact of the illness or who did not provide emotional support. They further suggested that the distress that confronts families can potentially impair the entire family unit, having a negative impact on the breast cancer patient. Findings will be disseminated and discussed within the Native Hawaiian community as well as prepared and submitted to a journal for publication.

- ***The Role of Traditional Healers in Cancer.*** A Native Samoan physician/investigator is examining how traditional Samoan healers can contribute to the assessment and management of patients with cancer.

An NCI-supported supplement builds on a collaborative research project addressing a major public health education priority of the National Strategic Plan for the Early Detection and Control of Breast and Cervical Cancers. The specific aims are to:

- Develop, implement and evaluate an innovative breast and cervical cancer control prevention education program specifically designed for American Samoan women.

- Identify cognitive, normative, social and structural factors that impede or facilitate behavior change. The study is being conducted in American Samoa and Los Angeles County, CA. The educational program will be evaluated in terms of its cultural sensitivity, linguistic appropriateness, and effectiveness in enhancing knowledge, affecting attitudes and modifying behaviors. The results of the study will provide crucial information for development of more comprehensive interventions.

Cancer Surveillance and Trends

The NCI Surveillance, Epidemiology, and End Results (SEER) Program collects and publishes cancer incidence and survival data from population-based cancer registries and supplemental registries. The recent expansion increased SEER coverage from 14 to 26 percent of the U.S. population (from about 39 million to nearly 74 million). With the expanded reporting beginning in 2003 (for 2000 data), this coverage will include 23 percent of African Americans, 40 percent of Hispanics (32 percent of non-Mexican Hispanics), 45 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of Native Hawaiians and Pacific Islanders.

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 SEER Program and cover the vast majority of Native Hawaiians. 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 2003 as population data from the 2000 census must be available by states in order to accurately calculate recent cancer rates.

The American Cancer Society, the National Cancer Institute, the North American Association of Central Cancer Registries, the National Institute on Aging, and the Centers for Disease Control and Prevention, including the National Center for Health Statistics, collaborate to provide an annual update on cancer occurrence and trends in the United States. The current *Annual Report to the Nation on the Status of Cancer Statistics, 1973 -1999,* published in May 2002, contains a special feature that focuses on the implications of age and aging on the U.S. cancer burden.

Age-specific cancer death rates for all sites combined for American Indian/Alaskan Native, Asian/Pacific Islander, and Hispanic populations were lower than for white and black populations. Asian/Pacific Islander women had the lowest age-specific death rates except for women under age 50. In the 2000 U.S. Census, the Asian/Pacific Islander (API) population makes up a higher proportion of the U.S. population compared to the 1990s. Within the API category, the composition of recent immigrants (by country of origin) is different from second generation APIs. These changes will have implications not only for the cancer burden as these populations grow and age, but also on a greater need for culturally appropriate prevention, early detection, and treatment programs.

Scientific Discovery

In fiscal year 2003, NCI will establish interdisciplinary research Centers for Population Health and Health Disparities to better understand the interaction of social, cultural, and physical environmental determinants of cancer incidence and outcomes and their behavioral and biologic mediators. Also supported by the National Institute of Environmental Sciences, the National Institute of Aging, and the Office of Behavioral and Social Sciences Research, this trans-NIH initiative will catalyze a new NCI focus on integrating the social and biologic sciences and

elucidating the basis of cancer-related health disparities in order to develop more effective interventions.

Clinical Trials

NCI has begun a Minority Accrual Initiative, whose goals include increasing the number of minority investigators and minority patients in cancer research. The University of Hawaii is one of the centers that have received additional funding to foster minority accrual to clinical trials through this initiative. Historically, the University of Hawaii and its affiliated hospitals have accrued large numbers of minority patients, both Asian-Americans and Native Hawaiians, to prevention and treatment trials.

Item

Chronic lymphocytic leukemia -- The Committee strongly encourages the NCI to increase the level of research aimed at determining the underlying cause and optimum therapies for CLL, the most common form of adult leukemia in the United States. The Committee is encouraged by the NCI's willingness to consider a supplementary application for research funding for the CLL Research Consortium. The Committee further urges the NCI to expand funding for the Consortium to speed up the progress in finding significant scientific breakthroughs. (p. 100)

Action taken or to be taken

On June 11-12, 2001, the National Cancer Institute (NCI) convened a State of the Science Meeting on Chronic Lymphocytic Leukemia. The report of this meeting is available at http://ctep.cancer.gov.

For the past 30 years, families with two or more living cases of chronic lymphocytic leukemia (CLL) have been enrolled within the NCI Familial Cancer Registry. Medical records and biological specimens have been collected for these subjects. Based on 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 have shown regions on certain chromosomes that may contain susceptibility genes, but these results need to be followed up in a larger sample. The regions on some of these chromosomes are of special interest because they overlap with cytogenetic abnormalities found in CLL tumor cells. Abnormalities in the ATM gene (named ATM for ataxia telangiectasia, mutated) in these families were looked at and four cases of abnormally low ATM protein expression were found. However, none of these cases had

a germ line mutation in the ATM gene. A collaboration is underway to conduct cytogenetic tests on material from the familial cases. Results show that consistent with sporadic CLL patients, nearly all of the familial cases have a deletion on chromosome 13q14. A putative precursor condition for CLL in these families, B-cell monoclonal lymphocytosis (BCML), has been documented and shown to occur more frequently in unaffected relatives of cases compared to the general population.

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 investigation as markers of disease progression. We found that CD38 does not predict survival, but telomere length is associated with survival and correlated with the presence of mutated immunoglobulin heavy chains.

Additional investigations planned are expansion of the familial CLL resource, expansion of the study of precursor conditions, analysis of additional candidate genes, and analysis of gene expression and protein patterns in CLL cells. In order to expand these studies, NCI investigators convened a meeting in September, 2002 to form an international consortium of investigators with an interest in familial CLL to collaborate and share data. The consortium will enrich ongoing scientific investigations by bringing together clinical investigators with genetic epidemiologists to pursue linkage studies and candidate gene approaches in order to determine the genetic underpinnings of CLL. NCI investigators are also collaborating with an NCI-funded extramural group, the CLL Research Consortium to add a familial CLL component to the overall project.

The CLL Research Consortium (CRC) continues to make significant progress on the genetic, biochemistry, immunobiology, pharmacology and clinical aspects of this disease. Several new proto-oncogenes that are over-expressed in CLL have been identified. One of these genes was placed under the control of B cell promoter/enhancer in transgenic mice. This mouse CLL model may allow investigators to study disease pathogenesis and perform preclinical evaluation of novel therapeutics in vivo.

Studies on the biochemical mechanisms that lead to drug resistance of leukemia cells to apoptosis has resulted in the identification of targets for development of novel approaches to therapy. Several histone deacetylase inhibitors have been identified that activate expression of genes encoding anti-apoptotic proteins. Furthermore, tubulin has been identified to undergo rapid turnover in leukemic cells. Interference with this turnover by agents can induce the release of several newly identified proteins that turn on the apoptotic pathways in the leukemia cell. While this may explain the clinical activity of such agents as vincristine, it also permits identification of novel compounds such as Indanocine that should have a higher therapeutic index in the treatment of patients with this disease.

“Nurse like cells” that protect leukemia cells from undergoing spontaneous or drug-induced apoptosis in vitro have been isolated. These cells differentiate from hematopoietic cells when in contact with CLL cells and are present at increased numbers in patients with CLL. This may account for the resistance of CLL cells to drugs or biologics in vivo. One recent interesting finding is that the anti-CD20 mAb Rituxamab had synergistic activity with glucocorticoids in

inducing apoptosis of CLL cells only in the presence of these "nurse-like cells." Thus the interaction between the nurse-like cells and CLL cells represents a novel target for therapeutic intervention. New combination therapy with drugs (nelarabine and fludarabine) and biologics (rituxamab and Hu1D10) are underdevelopment.

Using data from the Surveillance, Epidemiology and End Results (SEER) program, NCI scientists analyzed second cancers among 16,367 individuals with chronic lymphocytic leukemia. Solid tumors occurred in 1,820 persons. Risks were similar for patients regardless of whether they received chemotherapy only as the first course of treatment or no treatment initially. Significant excesses were found for Kaposi's sarcoma, malignant melanoma, laryngeal cancer, and lung cancer. Among men increased risks were found for brain cancer, and among women increases were found for cancers of the stomach and bladder. Risks of second cancers remained fairly constant throughout the follow-up period.

The NCI formed the Leukemia, Lymphoma, and Myeloma (LLM) Progress Review Group (PRG) to assess the state of the science for these cancers and make recommendations for future research. The PRG reported the findings from this review in May 2001. The report of the PRG is available at http://prg.nci.nih.gov/llm/default.html. This report identified areas that could be focused on to make progress against the blood cancers. The recommendations fell into 3 general groups:

- Understand the etiology and pathobiology of these diseases
- Support education, communication, and survivorship research
- Develop new treatments more rapidly and effectively through novel public-private partnerships

The NCI established a working group to respond to the recommendations of the PRG. In October 2002, the NCI released the Strategic Plan to Address the Recommendations of the Leukemia, Lymphoma, and Myeloma Progress Review Group (http://prg.nci.nih.gov/llm/llm.pdf). The Institute is now promoting the Strategic Plan within advocacy and research communities that focus on blood cancers.

This plan outlines the ongoing, new, and proposed strategies that the Institute has started or could pursue to make progress against these cancers. The ongoing activities identified in this plan are initiatives that the Institute is currently investing in that have some focus on the blood cancers. The new activities identified in the plan are initiatives that the Institute put in place after the release of the May 2001 report of the LLM PRG. The proposed strategies in the plan address important gaps in NCI's ongoing efforts. They fall into several categories. Immediate strategies are those that the Institute is currently working to implement. Short- and medium-term strategies are currently under development. These strategies need to be further refined and formal concepts need to be approved by the NCI leadership and the NCI's external advisory boards. Long-term strategies are not being developed at this time. However, the NCI is looking for partners in the community to help carry out or take the lead in the execution of many of these strategies.

Current NCI activities directly address recommendations made by the PRG and reflect the Institute's commitment to addressing gaps in research on blood cancers. This strategic plan is a call to action for the entire cancer research community. The NCI's LLM working group will

continue to oversee implementation and will help track progress in implementing the strategies outlined in the strategic plan.

Item

Complementary and alternative cancer therapies -- The Committee expects the NCI to expand its work and its collaborative efforts with NCCAM 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. 101)

Action taken or to be taken

The Office of Cancer Complementary and Alternative Medicine (OCCAM) of the National Cancer Institute (NCI) supports a broad research portfolio both on its own and in collaboration with the NIH National Center for Complementary and Alternative Medicine (NCCAM). OCCAM and NCCAM have released a call for applications for developmental grants in cancer complementary and alternative medicine. The intent of this initiative is to encourage and support the development of basic and clinical CAM cancer research and to provide the basis for more extended research projects by establishing the methodological feasibility and strengthening the scientific rationale for these projects.

The NCI and NCCAM each committed $1 million per year over three years to support high-quality programs at six NCI-designated Cancer Centers beginning in FY2001. The development of this program included the solicitation of applications and performance of a competitive review of pilot projects in any of a variety of CAM approaches. The research will be performed at comprehensive and clinical 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. The six NCI-designated Cancer Centers receiving awards with their first year research topics are:

Johns Hopkins Oncology Center

- Herbal Medicine for the Treatment of Esophageal Cancer
- Effects of Saw Palmetto on Prostate Cancer Tissue
- Mind-Body Therapy for Patients with Breast Cancer

Wake Forest School of Medicine

- Bee Propolis and its active ingredient caffeic acid phenethyl ester (CAPE) as radiosensitizing and pro-apoptotic agents for the treatment of prostate cancer
- Effect of Fish Oil Supplementation on Serum PSA levels in Health Men
- Lyc-O-Mato Tomato Extract and PSA response in men with biochemical relapse of prostate cancer following definitive local therapy
- Biomarker analysis

University of New Jersey Medicine and Dentistry
- The effect of glycyrrhiza Glabra in patients with Prostate Cancer
- The effects of curcuminoids and orange peel extract on aberrant crypt foci in the human colon
- The effect of green tea on therapy-induced mucositis and prevention of oral cancer in patients with leukplakia

University of Colorado Cancer Center
- Milk Thistle Extract for Prostate Cancer Intervention
- Grape Seed Extract as a preventive and therapeutic agent in breast carcinoma
- The Effect of Guided Imagery on Bone Marrow Transplant Patients

University of California at San Francisco Cancer Center and Cancer Research Institute
- Candidate Molecular Targets for Herb Cytotoxicity
- Traditional Chinese Medicine for Anal Dysplasia

University of Chicago Cancer Research Center
- Plasma concentrations of bioflavonoids and their effect on DNA-Damage of the MLL Gene in Breast Cancer Patients
- Antioxidant Herbs for Chemotherapy-Induced Emesis

NCI and NCCAM support a 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 September 2002, NCI increased funding for this study to permit the acquisition of some intermediate outcomes (i.e. changes in serum tumor markers and changes in tumor metabolic rate by PET scan).

In addition, the randomized, controlled clinical trials of oral shark cartilage for patients with lung cancer (MD Anderson Cancer Center Community Clinical Oncology Program) and breast or colorectal cancer (North Central Cancer Treatment Group, Mayo Clinic) are continuing to accrue patients.

NCI’s OCCAM and the Office of Cancer Communications, in conjunction with NCCAM, are continuing to produce fact sheets on CAM topics. These documents are written based on information contained in the NCI Physicians Data Query CAM summaries and can be accessed via OCCAM/NCCAM websites and the NCI Cancer Information Service.

NCI and NCCAM are collaborating in the planning and implementation of patient/caregiver telephone focus groups that will assist in assessing the CAM educational needs of this population. The information gathered from this process will help guide the development of educational pieces focusing on CAM and incorporating key messages about CAM use, including risks and benefits, into existing patient education material produced by both institutes.

OCCAM facilitates research programs and workshops to encourage high quality CAM research and the bridging of practice and research communities to form research partnerships. In fiscal year 2002, a total of six cancer center supplements were provided by NCI, five of which were in collaboration with NCCAM. A total of eleven clinical trial supplements were funded by the OCCAM and one additional supplement was funded by the NCI Division of Cancer Prevention. Seven grants supporting research on complementary and alternative medicine at the end-of-life for cancer and/or HIV/AIDS were funded, with NCI providing the primary funding for three of these grants and secondary funding for the other four. NCI also supported two grants focused on botanicals and drug interactions, one grant on older patient-physician-alternative healer relationships, one grant on the clinical significance for quality of life measures in oncology research, and one conference on integrative pain management.

OCCAM collaborates with NCI to provide supplementary funds to support CAM-related clinical trials, performed by the NCI's Cooperative Groups and Community Clinical Oncology Programs. The primary goal of this initiative is to support trials of approaches with greatest likelihood of providing benefit to cancer patients. There are currently two pilot studies, one Phase I/II study, three Phase II studies, and thirteen Phase III CAM studies underway within this program.

NCI is developing a funding mechanism focusing on integrative approaches to symptom management with the focus being to develop long term strategies for initiatives and activities to increase high quality symptom management research in both conventional and CAM topics.

OCCAM sponsored the first of a series of expert panel discussions in November 2001 that explored the major research methodology challenges in performing high-quality cancer CAM research. The panel which included researchers, physicians, statisticians, and nurses from leading cancer research and treatment centers reviewed the state of the science in the area of CAM cancer and symptom management and developed papers discussing the research design and methodology issues that often cause CAM grant applications to perform poorly in review. These papers have been submitted to a leading scientific journal and are undergoing peer review. The next panel discussion will be held in March 2003 focusing on botanicals.

OCCAM will be sponsoring a two-day Technical Assistance Workshop for investigators interested in cancer CAM research to be held in the Washington D.C. area. This two-day workshop, to be held in early 2003, is intended to assist researchers in the development of competitive 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 was held. The next seminar will be held in January 2003.

The OCCAM Best Case Series program affords opportunities for CAM practitioners to submit their best clinical case studies using alternative interventions. Medical records, diagnostic imaging, operative records, and pathology reports are submitted to the OCCAM which evaluates

and summarizes 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. NCI is promoting the Best Case Series program for CAM practitioners via direct mailings, conference sessions, and notices in conventional and CAM publications.

The Prospective Outcomes, Monitoring, and Evaluation (POMES) initiative focuses on an NCI-sponsored data gathering project at a homeopathic clinic in Calcutta, India. Presently, a Memo of Understanding between the OCCAM and this clinic is signed and a protocol describing the study is near completion.

The OCCAM disseminates information on CAM in a variety of ways. The OCCAM website (http://www3.cancer.gov/occam) provides a link with the general public; extramural/intramural research and practice communities; and other governmental agencies who are seeking updated information about NCI's CAM initiatives. The site contains updates of the status of current and planned OCCAM projects; funding opportunities; clinical trials; links to CAM information; information about the Best Case Series; and assistance on how to write NIH-sponsored grants. The website is evaluated on a monthly basis to ensure information is current and easily accessible by visitors of the site.

NCI anticipates supporting the Comprehensive Cancer Care V Conference, to be held in April 2003, via a grant to the Center for Mind-Body Medicine. The NCI will be present at this conference to discuss how to perform a best case series; opportunities for funding of CAM cancer research; symptom management; and how patients can most effectively utilize CAM therapies in conjunction with conventional cancer treatment.

OCCAM is in the process of developing two surveys targeting CAM practitioners and conventional cancer researchers. Survey results will be used to inform programmatic decision making; specifically, to guide the development of programs for both researchers and practitioners of CAM. The results will serve as a discussion base for developing and improving existing programs that will bridge the CAM practice community and the conventional cancer research community.

Item

DES -- The Committee continues to strongly support increased efforts to study and educate the public and health professionals about the impact of exposure to the synthetic hormone diethylstilbestrol (DES). The Committee expects the NCI to continue its support of research in this area. In addition, the Committee urges the NCI to continue its agreement with the CDC to implement a national education program for consumers and health professionals. The Committee expects the 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. 101)

Action taken or to be taken

In partnership with the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC) continues to lead 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, CDC, NCI, the HHS Office on Women's Health, and representatives of advocacy and health care provider organizations have worked together to plan and implement the campaign. The development phase of the campaign has been completed, the implementation phase began in 2002, and the dissemination phase will begin in early 2003.

CDC conducted formative research to assess target audiences' knowledge of DES-related health risks and health monitoring. Based on the research results, target audiences were identified, appropriate dissemination channels identified, draft materials for each audience were developed and pre-tested, and the campaign was renamed (CDC's DES Update). Target audiences for CDC's DES Update include a broad range of health care providers and consumers, including known-exposed individuals and those who may have been exposed but are unaware of their exposure status. Earlier DES education programs had targeted physicians only.

In 2001, materials were developed and pre-tested to meet the information needs for each target audience. Materials for health care providers in a variety of formats were developed in collaboration with medical and nursing school faculty at DHHS Centers for Excellence in Women's Health at Wake Forest University, University of Illinois at Chicago, MCP Hahnemann University, University of California at Los Angeles, and the University of Wisconsin. These materials were designed to be presented by clinicians and medical and nursing faculty in various medical education settings.

Materials developed for consumers will be available both in print and online and include a comprehensive set of fact sheets on DES history, research, resources, and health effects. In addition, the materials include instructions on how to interpret DES research, tips for talking with health care providers, and ways to track personal DES health history for known-exposed individuals and those unaware of their DES exposure. The consumer materials were developed in collaboration with the DES Working Group, including CDC and NCI staff, as well as representatives of advocacy and health care provider organizations.

The implementation phase began in 2002 with DES exhibits at 10 major national conferences of health care professional societies. The exhibits were designed to alert providers to the upcoming dissemination of DES materials to the public, explain DES-related health risks, describe the new materials and DES resources for health care providers. DES outreach to providers will continue

with the launch of CDC's DES Website in January 2003, a series of DES lectures and symposia planned to begin in 2003, introduction of DES curricula in medical and nursing schools, as well as web-based DES self-study and reference materials for clinicians.

Dissemination of materials for CDC's DES Update is scheduled to begin in early 2003. At that time, CDC's DES Website will be operational. All materials will be available through the website in downloadable form and can be ordered either online or through a toll-free CDC number in print or on CD-ROM. Additionally, the CDC is working with partner organizations serving target populations, as well as developing new partnerships with other related health-interest organizations, in order to disseminate DES materials to consumers.

A series of five teleconferences for the public, designed to meet information needs of known-exposed audiences is scheduled for 2003. DES researchers will discuss the latest research on 1) Breast Cancer Risks Associated with DES Exposure, 2) Latest Research on DES Sons, 3) Clear Cell Cancer Risks for DES Daughters, 4) Research on Reproductive Health Risks for DES Daughters, and 5) DES Animal Research.

CDC's DES Update will be evaluated at several points in time to assess change in knowledge, penetration of materials, and learning outcomes for target populations of consumers and health care professionals. A pre-campaign evaluation of DES knowledge, attitudes and behavior has been completed.

Women exposed prenatally to DES have an excess risk of clear cell adenocarcinoma of the vagina and cervix, but the effect of prenatal DES exposure on the incidence of squamous neoplasia is uncertain. A cohort of 3,899 exposed and 1,374 unexposed daughters was followed for 13 years (1982-1995) for pathology-confirmed diagnosis of high-grade squamous intraepithelial neoplasia of the genital tract. Based on 111 cases of high-grade disease, the relative risk of squamous neoplasia among DES-exposed daughters was twice as high as unexposed daughters. Risk estimates were higher with earlier intrauterine exposure, with the risk being three times higher for daughters exposed within 7 weeks of the mother's last menstrual period.

In a study of infertility, a total of 1,753 women exposed to DES prenatally and 1,050 unexposed women provided data on difficulties in conceiving and reasons for the difficulty. DES exposure was found to be significantly associated with infertility resulting from uterine or tubal problems.

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.

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. The follow-up should be completed in the Spring of 2003.

The NCI DES Follow-Up Study also serves as a specimen resource for laboratory scientists investigating any association of *in utero* exposure to hormones such as DES and subsequent neoplasms in susceptible individuals. A research team at Boston University has examined stored breast tissue from DES-exposed and unexposed women with breast cancer. Preliminary data indicate differences in certain molecular characteristics and DNA abnormalities related to DES exposure. This suggests that there could be molecular markers during breast cancer development that would be useful in cancer prevention strategies for individuals previously exposed to hormones such as DES. Investigators are expanding the study to examine larger numbers of specimens from women in the follow-up study and to incorporate state-of-the-art methods of analyses.

In response to concerns about possible multi-generational effects of DES exposure in humans, the Third Generation Study is underway to systematically follow the granddaughters of women who took DES during pregnancy. Launched in August 2000, the study intends to enroll 700 – 800 young women, two groups of adult daughters of mothers who were exposed to DES *in utero* and those whose mothers were not exposed. Study participants are being 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.

Investigators at the University of Chicago continue to maintain contact and obtain clinical and epidemiologic information on over 700 DES-exposed and unexposed women who have developed clear cell adenocarcinoma (CCA) of the vagina and/or cervix since 1971. A repository of malignant tissue has been established to provide the opportunity for basic research in molecular biology, genetics, and hormonal carcinogenesis. To date, analyses of cancer risk factors in CCA women indicate that pregnancy and use of oral contraceptives do not increase the risk of DES-exposed CCA. The CCA Registry will be further analyzing the characteristics and behavior of long-term survivors of CCA (preliminary findings first reported quality-of-life issues related to tumor recurrence, sexual and reproductive dysfunction, and emotional adjustments). Of particular interest is the question of what factors may increase the risk of secondary cancers and CCA recurrences in DES-exposed women.

Item

Gynecologic cancers -- The Committee is concerned about the patterns of care for gynecological cancers, and it urges the NCI to expand CanCORS to gynecologic cancers. While the Committee commends the NCI for funding four ovarian cancer SPOREs and the one gynecologic cancer SPORE, it believes research into other gynecologic cancers needs to be enhanced. The

Committee urges the NCI to continue funding ovarian cancer SPORES and to consider creating SPORES specifically for cervical and endometrial cancers. (p. 101)

Action taken or to be taken

The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) is a new initiative within the National Cancer Institute (NCI) to improve the methods and empirical base for quality of care assessment. The five-year cooperative agreement awards study the impact of targeted interventions on patient-centered outcomes, investigate dissemination of state-of-the-art therapies in the community, examine modifiable risk factors, and analyze disparities in quality of care. CanCORS supports large, prospective cohort studies of newly identified lung and colorectal cancer patients, with a target enrollment of 5,000 patients for each cancer type. Seven research teams from around the country are carrying out this NCI-coordinated effort, with support by a statistical coordinating center. Plans to reissue and expand CanCORS to other cancer sites including gynecologic cancers are under development.

The NCI also plans to expand the Gynecologic Cancer Specialized Programs of Research Excellence (SPOREs) for translational research in FY 2003. Six applications were reviewed in 2002 and two applications will be recommended for funding in FY 2003. One of the applications focuses on cervical cancer while the second application focuses on endometrial cancer. The NCI is planning an additional request for Gynecologic Cancer SPORE applications in 2004 and will consider the funding of such applications in FY 2005.

Furthermore, the NCI has worked to strengthen the Gynecologic Cancer Intergroup Committee (GCIG), which brings together representatives of all the Clinical Trials Cooperative Groups around the world which conduct clinical trials for women with gynecologic malignancies. One trial which has been developed evaluates three new drugs, gemcitabine, topotecan, and liposomal doxorubicin, in addition to carboplatin and paclitaxel in the primary treatment of ovarian cancer. This trial, which is now open in the United States, the United Kingdom, Australia, and Italy, will be the largest treatment trial in ovarian cancer conducted to date. So far, 1,500 of the planned 4,000 patients have been recruited to join this study, which is coordinated by the NCI-sponsored Gynecologic Oncology Group. Another major international trial evaluates the role of erythropoetin in maintaining hemoglobin levels among women undergoing chemoradiation for cervical cancer. Strengthening intergroup cooperation enables faster completion of clinical trials and identification of better therapies for women with gynecologic cancer more quickly.

Ovarian Cancer

NCI has plans to expand the Ovarian Cancer Specialized Programs of Research Excellence (SPOREs) for translational research, from four funded Ovarian Cancer SPOREs in 2002 to five SPOREs in 2003. The programs provide valuable infrastructure for translational research to develop new scientific approaches in early detection, diagnosis, treatment, and prognosis of human ovarian cancer.

An expanded network of ovarian SPOREs is performing an Inter-SPORE screening study for detection of ovarian cancer of women at high risk. The study is aimed at identifying specific gene clusters or genetic changes associated with normal, pre-neoplastic, and malignant lesions of the ovary. Delineation of the underlying molecular mechanisms involved in ovarian cancer progression may allow for a more accurate assessment of genetic risk, as well as identify potential diagnostic markers and therapeutic targets. Additional studies among ovarian SPOREs include collaborative research on chemoprevention clinical trials and search for biomarkers that will help in the early detection of ovarian cancer. The goal is to perform standardized screenings and a series of inter-related chemoprevention trials in women at high risk for ovarian cancer. The screening portion of the trial is aimed at establishing the normal ranges and distributions of CA-125 values within and between high-risk women and developing a repository of serial samples of serum, plasma, and white blood cells for biomarker analyses. This pilot study serves as a critical step towards validating a protocol for the early detection of ovarian cancer and provides an infrastructure for the addition of novel chemoprevention and treatment options for high-risk women.

A major approach in NCI studies has been to attempt to clarify the effects of environmental factors influencing cancer through examining effects within subgroups defined by genetic markers. These include various cancer-susceptibility genes known to affect either hormone or carcinogen metabolism. 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 and of physical activity. This study also has an extensive pathology 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.

A number of medical conditions have been suggested as predisposing to the risk of breast, endometrial and ovarian cancers, but most of these studies have relied on patients reports of these prior conditions. To obtain more precise information on the nature of these prior medical conditions, NCI scientists have conducted a large case-cohort study in Denmark that involves access to details of the conditions as contained in medical records. This study will enable a thorough assessment of cancer risk in relation to details of the prior diagnoses.

The NCI is carrying out a major evaluation of selected screening procedures for the early detection of prostate, lung, colon, and ovarian cancer (The PLCO Trial). The Trial will include 74,000 screening arm participants and an equal number of non-screened controls. Questionnaire data and biologic samples are collected in this population for use in studies on the etiology of breast cancers and for the evaluation of early markers of cancer development. Because of the prospective design, screening exams, and sequential pre-diagnostic blood sample collections, it will be possible to relate genetic, hormonal and other biomarkers to subsequent development of cancer.

In fiscal year 2002, NCI funded two grants that were focused on elucidating the basic biology of ovarian cancer. Investigators at the Fox Chase Cancer Center in Philadelphia are working on

generating a mouse model of ovarian cancer. The Gynecological Cancers Progress Review Group, an advisory committee to the NCI, has identified a need to develop good animal models to study ovarian cancer that mimic the human disease. It is known that the gene that codes for the protein Disabled-2 (Dab-2) is frequently lost in ovarian cancers and may be a tumor suppressor of ovarian cancer. Mice that lack the Dab-2 gene have been generated and the susceptibility of these mice to ovarian cancer is being examined. This mouse model will allow investigators to look at the biological role of the Dab-2 in ovarian cancers and elucidate how its loss contributes to tumor formation.

An investigator from the University of Worcester, Massachusetts will be testing the hypothesis that the protein CYP1A1 plays an important role in the development of ovarian cancers. CYP1A1 is an enzyme that catalyzes the conversion of carcinogen precursors into active carcinogens, including the conversion of the female hormone estrogen into a genotoxic form that could promote ovarian cancer. It is known that endogenous factors like estrogens as well as exogenous factors like environmental and diet-derived agents regulate CYP1A1activity in the body. The regulation of CYP1A1 under normal physiological conditions and whether its increased activity leads to ovarian cancers will be investigated. This will offer valuable insights into the development of the disease and lead to promising new targets for its treatment.

NCI investigators studying hereditary breast and ovarian cancer families (HBOC) will make clinical predictive genetic testing for BRCA1/2 mutations available to interested family members who have been participating in long-term research studies. All families have been notified of their mutation status, and the process of bringing interested family members to the NIH Clinical Center for genetic risk assessment, counseling, genetic testing and results disclosure is now underway. HBOC is the prototype inherited cancer disorder when it comes to translating the findings of laboratory research in cancer genetics into more effective modes of clinical practice.

Among the many pressing clinical issues in the management of women who carry mutations in BRCA1/2 is the appropriate role of oophorectomy as a risk reduction strategy for women at increased risk of ovarian cancer. NCI investigators, in collaboration with investigators from the Gynecologic Oncology Group (GOG) and the Cancer Genetics Network (CGN), have designed a national, prospective follow up study of genetically at risk women who elect to undergo risk-reducing oophorectomy. The following issues are being addressed: 1) what is the prevalence of clinically occult ovarian cancer at the time of risk-reducing oophorectomy; 2) are there identifiable precursor lesions in the ovaries of genetically at risk women; 3) what is the incidence of primary peritoneal carcinomatosis and breast cancer subsequent to this operation; and 4) how does this surgical procedure affect the quality of life for the women who elect it? Women who elect to retain their ovaries are being monitored with a novel ovarian cancer screening algorithm based on the rate of change of CA125 levels over time.

NCI scientists studied a 1979–1998 cohort of former participants in the Breast Cancer Detection Demonstration Project to determine whether hormone replacement therapy using estrogen only, estrogen-progestin only, or both estrogen only and estrogen-progestin increases ovarian cancer risk. Among 44,241 postmenopausal women, 329 women developed ovarian cancer during follow-up. Analyses showed that even use of estrogen only was significantly associated with

ovarian cancer, with increasing risk per year of use. The risks of ovarian cancer associated with less than 2 years and 2 or more years of estrogen-progestin-only use were 1.6 and 0.80, respectively, with no evidence of a duration response.

A retrospective cohort study of 12,000 women is nearing completion by NCI scientists to examine the effects on cancer risk of different causes of infertility and of different associated therapies. This study offers promise for disentangling ovulation-stimulating drug effects, particularly for ovarian cancer, from indications for usage. Since few studies have had careful clinical documentation of causes of infertility, the study has the potential for assessing why nulliparous women experience elevated risks of hormone-related cancers and of clarifying relationships of risk with such conditions as endometriosis and anovulation.

Cervical Cancer

More than 95% of cervical cancers are caused by the human papillomavirus (HPV). As we have learned more about how this virus causes cancers of the cervix, it has become clear that vaccine and immunologic approaches might help us prevent and/or cure many cases of cervical disease. Investigators at the NCI have worked closely to develop and evaluate vaccines to prevent HPV infection. In addtion, representatives from the NCI and the Food and Drug Administration (FDA) Center for Biologic Evaluation and Research continue to work closely to promote development and evaluation of therapeutic HPV vaccines, which are targeted to halt the development of cancer in women who have been infected with the HPV virus.

Previous studies from NCI investigators have suggested that, in addition to HPV infection, important determinants of cervical disease progression may include host immune response to HPV; exogenous and behavioral factors, such as parity and oral contraceptive use; and infection with sexually transmitted agents other than HPV. To further define the factors related to the progression of low-grade squamous intraepithelial lesions (LSIL), large cohort studies are being conducted in Costa Rica and in the United States. The Costa Rica cohort is a population-based study of 10,000 women. As part of this study, women with evidence of HPV infection, with or without LSIL, and a sample of the remaining cohort are being followed every six months to one year with repeat cytological screening, biological specimen collection, and assessment of risk factor profiles. Specific factors being evaluated include mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV.

A case-control study was conducted among women less than 50 years old enrolled in the Costa Rican natural history study of HPV and cervical neoplasia. A marginally significant positive trend of increasing cervical inflammation was associated with high-grade lesions in oncogenic HPV-infected women. Overt cervicitis was associated with a 1.9-fold increase in risk of high grade lesions. Cervical inflammation may be associated with high-grade lesions and may be an etiologic cofactor in women infected with oncogenic HPV.

The U.S.-based study, in which women are being seen at four clinical centers, is aimed at investigating specific immune responses to viral infection and risk of subsequent persistence

and/or progression of lesions. In this study, close to 1,000 women diagnosed with LSIL are being followed with repeat Pap smears, specimen collection, and risk factor assessment every six months for a period of two years. Biological samples are being tested for cellular and humoral responses to HPV to assess various immunological markers that may correlate with disease status over time.

NCI investigators have recently begun to determine the efficacy of two NCI-developed prophylactic and therapeutic HPV16 vaccines. Phase I and II trials were conducted in the United States, and a large efficacy Phase III trial will begin in early 2003 in Costa Rica in collaboration with the Costa Rican Ministry of Health. The prophylactic vaccines aim to reduce cervical cancer rates by preventing initial infections, while therapeutic vaccines are designed to target HPV-infected cells after the infection occurs. Demonstration that the HPV16 vaccines work would provide convincing proof-of-principle that could lead to efficient development of more comprehensive, multivalent vaccines by commercial entities.

NCI investigators have launched the first systematic clinical/genetic/epidemiologic study of the Inherited Bone Marrow Failure Syndromes of childhood. This group of disorders, for which Fanconi's anemia is the prototype, are well-known causes of bone marrow failure and acute leukemia in childhood. It has recently been recognized that, as affected children increasingly survive these early life illnesses, they are also at risk of a number of unusual solid cancers as young adults. Cancers of the uterine cervix, labia and anogenital region represent an important subset of these malignancies. Female members of families being studied at the NIH Clinical Center undergo a comprehensive gynecologic evaluation aimed at detecting pre-cancerous lesions and at investigating the role of HPV and other exposures in the pathogenesis of these cancers in genetically susceptible individuals.

Item

Imaging systems technologies -- The Committee is encouraged by progress made by the NCI following its August 1999 conference on biomedical imaging, and it urges the NCI to continue to take a leadership role with the Centers for Medicare and Medicaid Services (CMS) and the Food and Drug Administration to avoid duplicative reviews of new imaging technologies which may prevent their benefits from reaching patients on a timely basis. The Committee is aware of the great potential for improved patient care and disease management represented by molecular imaging technologies, especially positron emission tomography (PET) through its ability to image the biology of many kinds of cancer and other diseases. The Committee continues to support the 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. 101)

Action taken or to be taken

NCI funds approximately 37 investigator-initiated grants related to PET and micro-PET imaging technologies. Topics range from development of new detectors and system instrumentation to investigation of new agents for molecular imaging of cancer. 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. Twelve projects focus on investigation of new agents for molecular imaging of cancer. One project focuses on statistical methods for quantitative PET, and twelve 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 5 center grants to support "In vivo Cellular and Molecular Imaging Centers (ICMICs)" and 14 Pre-ICMIC planning grants. All of the centers, and the majority of the 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 to assess the androgen receptor, which is 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. Other investigators have been funded to begin assessing other PET agents such as fluorocholine and acetate which may improve the staging of prostate cancer.

Several PET studies are in progress for the evaluation, staging and monitoring of therapy using PET for women with breast cancer. Investigators at Johns Hopkins used F-18-fluorodeoxy glucose (FDG) to assess both the diagnostic utility and staging capabilities of PET. They are expected to publish their results in 2003. There are also several smaller clinical studies recently funded using FDG as well as newer PET compounds to measure proliferative activity of breast tumors and other important biological variables such as the estrogen receptor.

The American College of Radiology Imaging Network (ACRIN), an NCI funded cooperative group for imaging, is also performing two trials using FDG PET to monitor response to therapy. One trial is in small cell lung cancer and the other is in gastrointestinal stromal tumor (GIST). Some patients with GIST have had a remarkable response to the drug Gleevec, which was developed as an agent to directly target known metabolic pathways in this cancer. Not all patients with GIST tumors respond. Limited experience has demonstrated that changes in FDG-PET directly parallel the response to therapy with Gleevec. ACRIN investigators working with investigators in the Radiation Therapy Oncology group are further evaluating the biological effects of Gleevec on malignant GIST tumors with FDG-PET imaging in an ongoing trial.

In a large clinical trial at the University of Pennsylvania, dedicated breast PET will be incorporated 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.

The NCI is also developing protocols for early phase clinical trials using fluorocholine or carbon 11 acetate in patients with prostate cancer, and a fluorine 18 labeled PET tracer Fluoro-dihydrotestosterone (FDHT) to assess the androgen receptor in prostate cancer.

The NCI has recently signed a Cooperative Trials Agreement (CTA) with Advanced Magnetics Incorporated to study two different ultra-small superparamagnetic iron oxide particles using MRI in patients with both prostate and breast cancer. These MRI agents in very preliminary studies have been shown to significantly improve the accuracy for staging of lymph nodes in both prostate and breast cancer. This lymph node information is important in guiding the appropriate therapy for patients.

The NCI is sponsoring the Digital versus Film Screen Mammography Trial (DMIST), whose primary aim is to compare the diagnostic performance of digital mammography and screen-film mammography in a prospectively enrolled screening cohort of 49,500 asymptomatic women. The study will be performed at 24 centers in the U.S. and Canada and use all four digital mammography machine types currently in use. All women will undergo both digital and screen-film mammography. Breast cancer status for all participants will be determined either through the results of breast biopsy, if that occurs, or as a result of a year of follow-up without clinical evidence of disease.

The National Lung Screening Trial (NLST) aims to determine whether lung cancer screening using low-dose helical Computed Tomography (CT) reduces lung cancer-specific mortality relative to screening with standard chest radiography in a high-risk group of smokers. NLST is a prospective, randomized clinical trial. It is a combined project between the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial program and the American College of Radiology Imaging Network (ACRIN); an NCI sponsored Cooperative Group. The NLST trial will randomize approximately 50,000 subjects for study. Fifty percent of the participants will be randomized to annual spiral CT screening and 50 percent to annual chest radiograph screening. Participants will be selected from a high-risk cohort of smokers and former smokers between the ages of 55-74 at approximately 30 sites. All participants at all sites will receive an initial screen and two subsequent annual screens. Follow-up will include cancer incidence, cause of death, mortality impact and determination of adverse medical outcomes. Each study site will refer all eligible current smokers to local and National smoking cessation programs. Subsequent visits will reinforce the availability of these programs for participants still smoking or not participating in a smoking cessation program. The NLST was officially launched on September 18, 2002 by the President of the United States during a cancer prevention event at the White House and is currently enrolling participants.

The Radiation Oncology Molecular Assessment and Technology Center (ROMAT) is a proposed Center within the NCI intramural program. Its purpose would be to coordinate

molecular/functional imaging, molecular profiling and therapy, and technology development to study patients and their response to therapy at the molecular level. It would also be available as a unique collaborative resource for the nation's research institutions and corporations working with NCI through Cooperative Research and Development Agreements and other collaborative programs. The idea is to help accelerate the pathway from discovery to application while acquiring new knowledge. ROMAT will provide a locus for bringing together clinicians, biologists, engineers and physicists and to bring industry in as active collaborators.

NCI continues to be active in initiating, encouraging and facilitating interagency interactions relative to regulatory and reimbursement issues surrounding imaging technologies. 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. Since September 1999, NCI has co-sponsored with industry an annual national conference on biomedical imaging in oncology, called the National Forum on Biomedical Imaging in Oncology (NFBIO) that focuses on the research, regulatory, and reimbursement pathways of technology development. The Fourth NFBIO was held on Feb 6-7, 2003 (http://www3.cancer.gov/dctd/forum/). Topics have included the preclinical and clinical issues in molecular imaging as well as image-guided therapy, and the integration of in vitro techniques with in vivo imaging.

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 (ICBIO), consists of staff from the NCI, the Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (CMS) (http://www3.cancer.gov/scienceresources/announcements/imaging.html). 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. A variety of products from both large and small companies have been presented. The products include image acquisition devices, imaging agents, and software. The stage of development has ranged from early to mature technology. The feedback from the technology developers has been very positive.

These interagency activities have also facilitated discussions on areas of mutual interest for the agencies. For example, NCI and CMS continue to discuss how to address issues related to reimbursement for PET scans. The NCI has recently entered into Clinical Trial Agreements (CTAs) with 2 different companies related to imaging agents they are taking forward to the FDA. These companies invite NCI staff to attend and participate in the companies' discussions with the FDA about their specific data and questions.

Item

Kidney and bladder cancers -- The Committee is concerned that funding for kidney and bladder cancer has not kept pace with that of other cancers. The Committee understands that the NCI has worked with the scientific community to develop an agenda for research into these cancers. The

Committee encourages the NCI to implement this agenda for other urologic cancers in the coming fiscal year. (p. 101)

Action taken or to be taken

The National Cancer Institute conducted the Kidney/Bladder Progress Review Group (PRG) in November 2001. The PRG provided outside experts the opportunity to review progress, determine the current state of the science, and identify areas of research that NCI can support to advance progress against kidney/bladder cancers. From this information, approximately 125 experts and advocates from various disciplines made recommendations to advance kidney/bladder cancer research, including 10 high priorities. The report from this PRG is now available at http://planning.cancer.gov and is also available in hard copy.

In response to the report, NCI has created the Kidney/Bladder Cancers Working Group to fully review the research portfolio, identify gaps, and develop strategies for filling the most important of these gaps. NCI will publish these strategies in a strategic plan for addressing the PRG's recommendations. This plan will also outline the Institute's already existing initiatives addressing kidney and bladder cancers. The Report of the Kidney/Bladder Cancers PRG and the soon-to-be-developed strategic plan for implementation will be widely available so that academia, advocates, industry and national organizations can partner with the NCI in accelerating progress. The Kidney/Bladder Cancers Working Group will remain in place to oversee implementation and track progress, and a report on NCI's progress in implementing the recommendations will be available in 3-4 years.

Currently, the NCI has one Specialized Programs of Research Excellence (SPORE) in Genitourinary Cancers at the University of Texas, MD Anderson Cancer Center. The goal of the M.D. Anderson Genitourinary Cancer SPORE is to conduct innovative translational research in the prevention, detection, and treatment of urothelial cancer, leading to the eventual elimination of bladder cancer. This SPORE is comprised of a team of internationally recognized experts supported by the extensive translational research infrastructure that exists at M.D. Anderson. The complementary translational research projects of this SPORE should significantly expand our understanding of the genesis, progression, and metastasis of bladder cancer and help to contribute to the development of novel therapeutic strategies for the prevention, detection and treatment of this disease. This Bladder SPORE emphasizes five major multidisciplinary projects:

- ***Early detection and chemoprevention of bladder cancer.*** This project is testing the hypothesis that genetic and protein alterations serve as signatures of bladder cancer and can be used for the early detection of bladder cancer and as indicators for progression. This is to lead to the identification of novel surrogate endpoint biomarkers for chemoprevention and for the identification of individuals that would benefit from novel therapeutic strategies (such as gene therapy).

- ***Epidemiology of bladder cancer recurrence***. This project evaluates the epidemiological profiles and a panel of genotypic susceptibility markers related to tobacco carcinogen metabolism, DNA repair, disease progression, and nicotine addiction in the risk of recurrence

in patients with superficial bladder cancer. The clear identification of risk factors for bladder cancer should markedly facilitate the development of new strategies for the primary and secondary prevention of bladder cancer.

- ***Death receptors in bladder cancer progression and therapy***. This project tests the hypothesis that sensitivity to the induction of apoptotic cell death through "death receptors" participates substantially in interferon-induced tumor regression, and that the loss of death receptor sensitivity occurs during tumor progression. This study explores numerous molecular mechanisms through which tumor cell killing may be induced.

- ***Biology and therapeutic targeting of the epidermal growth factor receptor in bladder cancer.*** The purpose of this project is to delineate the cellular and molecular mechanisms by which growth factor signal transduction regulates invasion, angiogenesis, and metastasis of bladder cancer. Therapy that will target the epidermal growth factor receptor will be evaluated for patients with advanced bladder cancer.

- ***Improving gene therapy for superficial bladder cancer***. This project will utilize preclinical models of intravesical gene therapy to investigate this treatment as a strategy for bladder salvage for patients whose superficial TCC has failed standard intravescicular therapy.

This SPORE in Bladder cancer also includes a career development program that trains physician-scientists to formulate research plans with clinically testable hypotheses and a developmental research program designed to support pilot projects in bladder cancer research. This SPORE has also established an administrative core which facilitates interactions among the investigators, and a biostatistical and data management core, which serves multiple needs for the planning and conduct of the SPORE's translational research, providing innovative statistical modeling and data analysis, and ensuring that the results of all projects are based on well-designed experiments. The tissue resource and pathology core of this SPORE in Bladder Cancer provides the investigators at the M.D. Anderson Cancer Center as well as other collaborating institutions with high-quality tissue samples from patients that have been diagnosed, treated and closely followed for bladder cancer.

In addition, the NCI has implemented a number of initiatives that address kidney and bladder cancers:

- ***Pilot and Feasibility Program in Urology.*** The primary intent of this initiative, sponsored by the National Institute of Diabetes, Digestive, and Kidney Diseases and the NCI, is to foster the development of high-risk pilot and feasibility research by newly independent or established investigators developing a new line of research. Information thus obtained would allow subsequent submission of R01 applications focusing on research problems relevant to the study of urologic diseases and their complications.

- ***Pilot and Feasibility Program Related to the Kidney.*** The National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the NCI invite applications from investigators with research interests related to the kidney and fall within the

purview of the NIH mission. The primary intent of this initiative is to foster the development of high-risk pilot and feasibility research by newly independent or established investigators, to develop new ideas sufficiently to allow for subsequent submission of R01 applications focusing on research problems relevant to the study of both acute and chronic kidney diseases, and their complications, in both the adult and pediatric populations.

- ***Quick Trials for Novel Cancer Therapies.*** The Quick Trials program was conceived to speed the translation of ideas developed in the laboratory to early stage clinical trials by simplifying the grant application process and providing a rapid turnaround from application to funding. Initially developed as a pilot program in prostate cancer, this successful initiative has been expanded to address all cancer sites and provide funding to test and develop novel cancer therapies.

- ***Clinical Cancer Therapy Research.*** This initiative supports grant applications to conduct clinical therapeutic studies/trials of cancer in humans. This program announcement (PA) encompasses a full range of therapeutic studies and clinical trials employing drugs, biologics, radiation, and surgery. The intent of the PA is to encourage clinical researchers to translate insights in cancer biology and the development of new agents into innovative cancer therapeutic studies. The rate of progress in the treatment of cancer depends upon the translation of these basic and preclinical discoveries into clinical cancer therapies.

- ***O'Brien Urology Research Centers (NIDDK initiative co-funded by NCI).*** The major emphasis of these centers is to understand normal growth and the development processes of the urinary tract, as well as the development of both non-malignant and malignant disorders.

Ongoing research within NCI's Intramural Program includes:

- ***Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC).*** NCI is studying this hereditary kidney cancer syndrome in which the affected individuals are at risk for the development of kidney tumors, skin tumors, and uterine leiomyomas (fibroids) and uterine leiomyosarcoma. NCI has demonstrated that there are mutations of a gene called fumarate hydrase (FH) in the germline of HLRCC patients. The biochemistry of these genes, i.e., how damage to these genes leads to cancer, are being studied to develop new therapeutic strategies for patients with these diseases.

- ***African Americans and Kidney Cancer.*** Kidney cancer is increasing at a rate of 2.5 percent per year in the U.S., and it is increasing fastest in the African American population. NCI will attempt to determine if there is a very different histologic spectrum of kidney cancer in the African American community. Both the types of kidney cancers and reasons for accelerated rates need to be explained.

- ***Heriditary Aspects.*** Recent studies suggest that up to 68 percent of "sporadic" kidney cancer is actually hereditary. Therefore, NCI has launched a nationwide and international study to identify the genetic basis of this new form of inherited kidney cancer.

- ***Treatment.*** NCI is currently testing small molecules that block kidney cancer pathways and will evaluate these or related compounds in patients with advanced cancer of the kidney. NCI is also evaluating the role of anti-angiogenic therapies in patients with kidney cancer as well as combinations of immunologic agents, such as IL-2.

- ***Allogeneic Stem Cell Transplantation Therapy.*** Studies are underway to evaluate the role of allogeneic stem cell transplantation therapy in patients with advanced renal carcinoma. In a preliminary study, nearly 60 percent of patients with advanced clear cell renal carcinoma responded to this form of therapy.

Item

Liver cancer -- The Committee encourages the NCI to work closely with the NIDDK to investigate prevention, diagnosis and therapy for hepatocellular carcinoma and other cancers of the liver. (p. 102)

Action taken or to be taken

Hepatocellular carcinoma (HCC) is a common and rapidly fatal cancer. Worldwide, there are an estimated 437,000 new cases diagnosed annually. It ranks fourth in terms of mortality, behind lung, stomach and colon cancers. Over 90% of primary carcinomas of the liver are hepatocellular carcinomas. Recent studies indicate that the incidence of HCC in the United States is rising, while the rates of most other cancers are declining. This increased incidence is most pronounced in the African-American population. These trends further emphasize the need for the continued study of liver cancer.

The National Cancer Institute (NCI) continues to collaborate with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and other NIH Institutes and Centers (ICs) to sponsor research activities to prevent, diagnose and treat liver cancer and to promote scientific conferences to exchange information about liver cancer. The NCI is actively involved in the support of studies of the etiology and epidemiology of hepatocellular carcinoma. Through its interactions with the other participating NIH ICs, including NIDDK, NCI has co-sponsored ongoing clinical trials, research activities and conferences that contribute significantly to our knowledge of Hepatitis C Virus (HCV) and its associated liver diseases, including cancer. These cooperative activities result in the development of a research program that maximizes return on research funding by cooperative interaction with other NIH ICs and co-funding research activities of mutual interest to address important overarching scientific issues beyond the scope of any one NIH Institute or Center.

The NCI co-sponsored an NIH Consensus Development Conference “Management of Hepatitis C: 2002” along with NIDDK and other NIH ICs. This conference was held June 10-12, 2002, and was a follow up to the 1997 Consensus Development Conference on HCV. The conference highlighted the current state of knowledge about the management of HCV infections and associated diseases including liver cancer. The major topics of the conference included: natural history of HCV; approaches to diagnosing and monitoring patients; effective therapies for HCV;

which patients with HCV should be treated; how HCV transmission can be prevented; and identification of the most important areas for future research. As a result of this conference, the NIDDK is issuing a request for grant applications (RFA) to stimulate research in the natural history, pathogenesis, therapy and prevention of HCV associated liver diseases including liver cancer. The NCI will be co-sponsoring this RFA and providing funds to support high-quality applications relevant to liver cancer.

As part of its efforts to better understand this disease, NCI scientists organized an International Workshop on Molecular Pathogenesis of Human Hepatocellular Carcinoma, which was held on the NIH campus in September 2002. This workshop brought together leading US and foreign experts in the field of liver cancer, and provided a forum for both intramural and extramural scientists. The goal of the conference was to foster a better understanding of the latest research findings and implementation of these findings in diagnosis, treatment, and prevention of liver cancer. Intramural scientists from both NCI and NIDDK were active participants in this conference. NCI investigators have established collaborations with NIDDK investigators to study the gene expression profiles of livers expressing the HBx protein of the oncogenic hepatitis B virus. Since hepatitis B and C viruses are two major risk factors associated with hepatocellular carcinoma, this research is also focused on studying the mechanisms of oncogenicity associated with these two viruses, with the goal of decreasing liver cancer aggressiveness and increasing patient survival.

The NCI continues to be actively involved in the NIH hepatitis C virus working group. Congressional appropriations report language in 1997 requested that the NIH form a working group whose charge would be to develop an integrated NIH-wide plan for hepatitis C. Meetings have generally been held monthly, with representation from the National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infection Diseases (NIAID), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), the National Heart, Lung, and Blood Institute (NHLBI), and the National Center for Research Resources (NCRR), along with the National Center for Complementary and Alternative Medicine (NCCAM), the NIH Center for Scientific Review, and the Office of Research on Minority Health (ORMH).

The working group=s functions are to: share information about current activities in order to develop collaborations; foster the development of individual institute research agendas; focus attention on specific areas of research through meetings and workshops; and develop new initiatives that address this agenda and encourage participation of multiple ICs as appropriate. NCI continues to contribute significantly to these goals.

NCI is co-sponsoring an NIDDK randomized clinical trial, the HALT-C trial (Hepatitis C Antiviral Long-term Treatment against Cirrhosis). The purpose of this trial is to decrease the risk of adverse outcomes from chronic HCV infection, including HCC. The study is designed to determine if continuing interferon treatment over several years will suppress HCV, prevent progression to cirrhosis, prevent liver cancer and reduce the need for liver transplantation. Subjects are HCV-infected patients who have failed initial therapy for HCV. Half of the patients in HALT-C will receive treatment with long acting interferon for 42 months and the other half

will receive no long-term treatment. NCI scientists have been working to incorporate markers of genetic susceptibility as well as a nutritional component into the trial. The HALT-C trial has the potential to produce important information about treatment for the nearly half of the HCV-infected patients who fail initial therapy. Improved treatment should reduce the incidence of HCC and chronic liver disease due to HCV infection.

In another collaboration, NCI and NIDDK scientists are conducting a study of injection drug users who have failed to become infected with HCV despite many years of drug injection. It is hypothesized that such people may have genetic or immunological protection against HCV infection, the discovery of which could lead to better treatment or prevention of HCV infection in other persons.

HCV infection is common in some groups of HIV – infected persons, such as intravenous drug users and patients with hemophilia. NCI scientists examined the relationship between HCV and HCC by comparing the risk for this cancer in various HIV risk groups. Risk for HCC was highest in groups with high HCV prevalence, suggesting that this virus causes cancer among persons with AIDS. Notably, however, even in groups with low HCV prevalence, HCC risk was higher than that of the general population.

The most common life-threatening complication of HCV infection is cirrhosis and ultimately end-stage liver disease. Cirrhosis is often a precursor to HCC as well as to end-stage liver disease. In the first Multicenter Hemophilia Cohort Study, NCI scientists showed increased HCV viral load among hemophiliacs coinfected with HIV compared with those infected with HCV alone. They also showed that the risk of end-stage liver disease was increased eight-fold for those with HIV as well as HCV. Paradoxically, the risk of end-stage liver disease was not related to HCV viral load, suggesting a non-viral effect, such as an aberrant immunologic response, was leading to cirrhosis and disease. To intensify these investigations, and to broaden them to conditions such as non-Hodgkin's lymphoma that may be related to HCV infection, the NCI initiated a Second Multicenter Hemophilia Cohort Study (MHCS-II) that has enrolled more than 1300 persons with hemophilia at 40 collaborating hemophilia treatment centers. Initial reports from MHCS-II are anticipated during 2003.

NCI investigators are examining the prevalence of HCV in a representative sample of the population in Linxian, China. A high prevalence of HCV infection has been found that is consistent with press reports that blood-borne viruses are being transmitted at high rates in rural China.

Biliary tract cancer, which encompasses cancers of the gallbladder, extrahepatic bile duct, and ampulla of Vater, is a rare cancer. Other than gallstones, the etiology of biliary tract cancer is poorly understood. In Shanghai, China, the incidence of biliary tract cancer is rising more rapidly than the incidence of any other malignancy. As in other countries, gallbladder cancer is the most common subsite and occurs more often among women than men. To further elucidate the etiology of biliary tract cancer and reasons for the rapid increase in incidence, NCI scientists have joined forces with the Shanghai Cancer Institute and launched a collaborative study of biliary tract cancer.

This complex, multidisciplinary, population-based case-control study is the largest and most comprehensive ever for biliary tract cancer. The study enrolled nearly 3,000 persons, including 891 case subjects with cancer, 1,035 control subjects with gallstones, and 1,005 healthy subjects randomly selected from the population. The study has an extensive biochemical and molecular component, with more than 85 percent of the subjects providing 20 mL of fasting blood and 24-hour urine samples, along with the collection of bile samples, gallstones, and fresh and fixed tissue samples from patients undergoing surgical resection of the biliary tract.

Data collection was successfully completed in July 2001. More than 45,000 vials of biological specimens, including 26,000 vials of DNA samples, have been stored for examination. Collaboration with the Shanghai Cancer Institute, MD Anderson Cancer Center, Johns Hopkins University, Massachusetts Institute of Technology, and Wake Forest Genome Center is actively under way to evaluate several key etiologic hypotheses as well as genetic susceptibility related to lipid and hormone metabolism.

The NCI–China Collaborative Biliary Tract Cancer Study provides a unique opportunity to uncover the etiology of biliary tract cancer. The extensive collection of epidemiologic and clinical data along with biological specimens represents a rich resource to test emerging etiologic hypotheses with state-of-the art techniques.

Item

[NF Research Portfolio] -- The Committee encourages the 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. 102)

Action taken or to be taken

Neurofibromatosis type 1 (NF1) is a common inherited disorder, which affects 1 out of every 3,000 people (>80,000 persons affected in the United States). NF1 is characterized by a number of progressive changes of the skin, nervous system, and skeleton. Patients with NF1 have an increased risk of developing benign and malignant tumors of the nervous system.

Plexiform neurofibromas are tumors which arise from the outer layer of nerves and occur in approximately 25% of patients with NF1. They grow along the length of nerves within the skin or deep inside the body and involve multiple branches of a nerve. Plexiform neurofibromas are a major source of pain, disfigurement, and impairment of nerve function. In some cases, they may develop into malignant tumors. Plexiform neurofibromas that cause significant problems are treated by surgical removal. However, most of the tumors cannot be removed completely, and up to 44% of tumors regrow after the first surgery. There is no other standard treatment for patients with NF1 and progressive plexiform neurofibromas.

The Pediatric Oncology Branch (POB) of the National Cancer Institute (NCI) has a long-standing interest in the development of new treatments for patients with treatment refractory cancers, and has recognized the need to extend these treatments to patients with NF1. Clinical trials with the

drugs phenylacetate and phenylbutyrate were open to patients with NF1 and progressive plexiform neurofibromas and to children with refractory cancers. Both drugs work by changing the behavior of tumor cells rather than by killing tumor cells as standard chemotherapy agents do.

Recently, a more targeted approach for the treatment of progressive plexiform neurofibromas has become available and is being studied by the NCI. 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.

R115777 is a new experimental drug that interferes with the function of the *ras* protein and other proteins in cells by blocking a step in the formation of these proteins. R115777 can block the growth of cancer cells and of tumor cells derived from patients with NF1 in test tubes and in animals. This experimental drug has completed evaluation in early clinical trials for adults. At tolerable doses of R115777, a 30% response rate was observed in adult patients with treatment refractory leukemias, and responses were observed in adults with solid tumors.

In collaboration with the Children's Hospital & Medical Center, Cincinnati, OH, and the Texas Children's Hospital, Houston, TX, the NCI has recently completed a phase I trial of R115777 for children with refractory cancers and with NF1 and progressive, plexiform neurofibromas. This was the only clinical trial with the new class of agents to include patients with NF1. The goal of this trial was to study the toxicities and pharmacokinetics (how the patient's body handles the drug) of R115777, and to determine the optimal dose of R115777. Seventeen patients with NF1 were enrolled on this trial. No objective responses were documented, but six patients reported a decrease in discomfort/pain after starting R115777, and one patient had healing of chronic skin breakdown overlying a large plexiform neurofibroma.

Based on the results of the phase I trial of R115777 in children with NF1, the NCI has opened a phase II trial of R115777 for patients with NF1. Patients 3-25 years of age and younger with measurable, growing plexiform neurofibromas that cannot be completely surgically resected are eligible for this trial. The main purposes of this research study are to (1) determine if R115777 can slow down the growth rate of plexiform neurofibromas in patients with NF1, (2) determine if R115777 can result in shrinkage of progressive plexiform neurofibromas, (3) determine the types of side effects that can be produced by R115777 in children and young adults with NF1, and (4) study the biology of the tumors from patients with NF1.

Unlike cancers, the growth of plexiform neurofibromas is unpredictable, and can include periods of rapid growth or long periods of quiescence. Some plexiform neurofibromas remain static indefinitely after a period of active growth. This erratic behavior can make it difficult to measure the effectiveness of R115777 as a treatment for plexiform neurofibromas. In order to find out if

R115777 will be helpful for patients with plexiform neurofibromas, the effects of the drug are compared to a placebo (a similar tablet that does not contain R115777) in each patient who is treated on the study. Before starting any treatment it is randomly determined whether the patient initially receives either R115777 or placebo. Patients are followed closely throughout the study for signs of increase of the neurofibroma by clinical examinations, photography of visible tumors and MRI scans. If the plexiform neurofibromas are increasing in size, the patient is switched to the other treatment (from placebo to R115777 or vice versa). Should the tumor be stable or decrease in size, the patient continues to receive the same treatment for as long as it is well tolerated and appears to be of benefit. The design of this study is complicated, but will hopefully offer the best chance of determining if R115777 is of benefit for progressive plexiform neurofibromas. This trial has received a "Clinical Trial Award" from the U.S. Department of Defense, and 14 patients have been enrolled since August 2002.

The NCI POB is also participating in an ongoing multi-institutional study to assess the natural history of patients with NF1 and plexiform neurofibromas. This study is coordinated by the Partners Center of Human Genetics in Boston, MA. The primary goals are to study the natural history of plexiform neurofibromas and to evaluate the usefulness of volumetric tumor measurements in this disease. Other goals of the Natural History Protocol are to establish a tissue bank, in which tissue samples obtained on the protocol will be made available to investigators after appropriate review. Clinical information about patients is entered in a central database. Participation in this trial allows the NCI to expand our experience with NF1. In addition, patients who develop disease progression will likely be eligible for participation in the phase II trial of R115777.

Pirfenidone is a novel anti-fibrotic agent with activity in fibrosing conditions. Gene profile analysis of plexiform neurofibromas in patients with NF1 demonstrates overexpression of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor. Pirfenidone inhibits these and other growth factors. Pirfenidone is presently under study in a phase II trial for adults with progressive plexiform neurofibromas at the Mayo Clinic.

In collaboration with the Children's National Medical Center in Washington, DC and the Mayo Clinic in Rochester, Minnesota, the NCI will coordinate a phase I trial of pirfenidone for children with NF1 and plexiform neurofibromas to determine the optimal dose, toxicities, and pharmacokinetics of pirfenidone. After completion of the phase I trial, the plan is to initiate a phase II trial for children with NF1 and progressive plexiform neurofibromas to assess the potential benefit of pirfenidone in this population. This trial will soon be open for enrollment, and 14 institutions will participate in this trial.

The NCI is interested in the development of a phase I trial of BAY 43-9006 for patients with refractory solid tumors and NF1 and plexiform neurofibromas. BAY 43-9006 is an inhibitor of Raf1 kinase, a downstream target of Ras, and has completed evaluation in early clinical trials for adults with solid tumors. Upon completion of the phase I trial the plan would be to develop a phase II trial for patients with NF1 and progressive plexiform neurofibromas. Should new treatment modalities be promising, these agents will be evaluated for the treatment of other disease manifestations of NF1 such as optic nerve tumors or dermal neurofibromas.

NCI also supports clinical trials through the pediatric clinical trials cooperative group that specifically include children with cancers associated with NF1. Of special relevance 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 for children younger than 10 years of age with progressive low grade astrocytoma. Approximately 260 children have now been entered into this study, and at current rates of accrual, the study should complete patient enrollment in less than 2 years. The primary objective of the study is to compare event-free-survival 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.

NCI scientists began studies of neurofibromatosis 2 (NF2) in 1987. This disorder is characterized by development of bilateral vestibular schwannomas, 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 an 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 molecular genetic studies of blood samples.

Many patients with NF2 develop a variety of ocular abnormalities in addition to central and peripheral nervous system tumors. Investigators from the NCI, the National Eye Institute (NEI), the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS) examined 40 ocular lesions from four deceased NF2 patients to determine the role of the NF2 gene. The investigators compared the number of copies of DNA markers on either side of the NF2 gene in normal and abnormal ocular tissue. The scientists determined that the loss of function of the NF2 gene was the mechanism that leads to the ocular lesions. The same mechanism is also associated with the development of nervous system tumors in NF2 patients.

Individuals with a disorder caused by mutations in a single gene often differ in the extent to which the disorder affects them. The difference in clinical manifestations may be caused by chance, by modifying genes at other locations in the genome, by environmental exposures or by some combination of these factors. An NCI investigator contributed clinical data on a series of NF2 patients to a collaborative project involving extramural scientists from the U.S., Canada, England and Germany. The purpose of the project was to use a variety of statistical approaches to estimate correlations between family members with NF2 for a number of different clinical endpoints. The data were based on 390 NF2 patients from 153 unrelated families. The analyses demonstrated significant intrafamilial correlations for age at onset of symptoms associated with NF2, age at hearing loss, and number of meningiomas (benign tumors) within the brain. These

results indicate that relatives with NF2 have specific clinical features that are more similar to each other than to unrelated individuals with NF2. These correlations may be due to effects of the specific mutation in each family, shared modifying genes or environmental exposures. However, the investigators observed similar and even greater intrafamilial correlations for each clinical feature when they compared subgroups of NF2 patients with the same general type of mutation. These results cannot differentiate between the role of specific NF2 mutations and the effects of modifying genes. To provide more insight into the causes of clinical variability, other statistical methodologies are needed that can assess the role of both genetic and environmental factors at the same time.

Item

[Proteomic Analysis] -- The Committee further notes the promise of utilizing proteomic analysis of blood samples to diagnose pancreatic cancer at its earliest stages. Proteomic analysis, which involves the identification of specific protein patterns in blood or other specimens that match known malignant patterns, is quicker than identifying separate proteins and the genes that create the proteins. This analysis was recently employed for the detection of ovarian neoplasms and is presently under study for the early detection of invasive prostate cancer. The Committee encourages the NCI to rapidly identify predictive proteomic patterns relevant to pancreatic cancer. (p.102)

Action taken or to be taken

Proteomics is the study of the proteins produced by cells. New technologies that allow researchers to visualize thousands of proteins at the same time can reveal patterns that may have important clinical implications. Combining proteomic technology with artificial intelligence based bioinformatics can be a powerful tool, and is a new paradigm in the detection and diagnosis of both ovarian and prostate cancers. In the future, this new approach may prove useful in detecting and diagnosing many other cancers and diseases. This includes some of the most common and lethal human tumors – breast, pancreatic, colon and lung.

Currently, proteomic technology is playing an important role in two clinical trials for ovarian cancer sponsored by the National Cancer Institute (NCI). The first of these trials is an observational study investigating whether protein patterns can be used to predict recurrence of disease before clinical symptoms appear. A second trial will use proteomics to increase the understanding of how a cancer drug works. Correlating protein patterns with clinical outcomes of treatment may allow researchers to predict which patients are likely to have an early toxic response so that they can be treated at lower doses or switched to a new therapy choice.

Using this technology may also help distinguish between prostate cancer and benign conditions. By identifying patterns of proteins found in patients' blood serum, researchers were able to differentiate between samples taken from patients diagnosed with cancer and those from patients diagnosed with benign prostate disease. The technique proved effective not only in men with normal and high PSA levels, but also in those whose PSA levels were marginally elevated.

Researchers believe the analysis of protein patterns will be a useful tool in the future for deciding whether men with marginally elevated PSA levels should undergo biopsy.

Improved methods for early diagnosis of pancreatic cancer can potentially have a profound impact by reducing the suffering and death caused by this insidious type of cancer. Accordingly, within the Clinical Proteomics Program directed by the NCI and the Food and Drug Administration (FDA), researchers have already begun to study serum samples from patients afflicted with various stages of pancreatic cancer. Preliminary results indicate that serum proteomic patterns may contain signatures which correlate with the presence of pancreatic cancer. The NCI plans to further expand and extend the application of proteomic patterns to pancreatic cancer in parallel with the ongoing work on ovarian, prostate and breast cancer.

Item

Primary immunodeficiencies (PI) -- Research has shown that patients suffering from primary immunodeficiencies have a 100-200 times greater risk of developing cancer than persons not suffering from PI. This has been a particular problem in minority communities, where PI is often underdiagnosed. The Committee urges the NCI to fund an aggressive research agenda that will target methods of identifying undiagnosed patients and appropriate treatments as a means of preventing cancer. In addition, the Committee continues to urge NCI to play a meaningful role in the national physician education and public awareness campaign of the Jeffrey Modell Foundation. (p. 102)

Action taken or to be taken

The National Cancer Institute (NCI) is highly interested in the relation between primary immune deficiency diseases (PID) and cancer. Data from statistical studies indicate a 100-200 fold increase in PID patients and development of cancer. This seems to be particularly true in hematologic malignancies such as leukemias and lymphomas. In addition, the data indicate a higher incidence of cancers in minority populations. These under-served populations, especially children, may have undiagnosed PID. Recent studies as well as results of a March 2000 meeting on PID and cancer, emphasized the need to focus on screening under-served populations. The co-founders of the Jeffrey Modell Foundation participated in the meeting and endorsed the focus of PID and cancer in under-served populations, especially children.

As a result, the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD) are co-funding a grant focused on PID in under-served populations. This study is looking at diagnosis in under-served populations and may also provide insights into the etiology of cancers, particularly leukemias and lymphomas, within under-served populations.

In addition, NCI has encouraged increased outreach to health care providers within clinical facilities. The outreach program is intended to enhance clinical diagnosis of PID in Hispanic and African Americans. The study employs bilingual health care providers and provides them with educational materials in both Spanish and English.

Plans are underway to have the Jeffrey Modell Foundation web page linked to the NCI web page. The ultimate goal of these efforts is to acquaint health care providers with information on symptoms of PID to be more alert to patients from under-served populations who may present with symptoms of PID and to initiate prompt treatment to reduce the incidence of cancer in minority patients.

NCI intramural scientists are active in a number of national and international organizations with a special interest in primary immune deficiency diseases. NCI scientists are major participants in the scientific advisory boards of the Pan American Group for Immunodeficiency Diseases (PAGID), and the European Society for Immunodeficiencies (ESID), both organizations dedicated to the study of primary immune deficiency diseases. These scientists also participate in the Jeffrey Modell Foundation, are on the Medical Advisory Board of the International Patient Organization of Primary Immunodeficiencies (IPOPI), and are on the NIAID Task Force on Immunology. From its inception three decades ago, select intramural NCI scientists have been active as members of the scientific committee on primary immune deficiency diseases organized by the International Union of Immunological Societies (IUIS), an international non-governmental organization in official relations with the World Health Organization (WHO).

The International AIDS Malignancy Conference organized by the NCI has been expanded to include malignancies occurring in a variety of immunodeficiencies, including primary immunodeficiencies. This is now reflected in its title: 7th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic and Clinical Research. The NCI intramural program has also formed an HIV and Cancer Virology Faculty with the focus being HIV and tumor virology. This applies to primary immunodeficiency diseases, as the tumors that arise in such patients are generally caused by viruses. Therefore, because the tumors that arise in primary immunodeficiency are similar to those that arise in AIDS, research in one area will help advance research in the other.

The NCI is also funding a number of new research initiatives. These include:

- Studies of the gene defective in the X-linked lymphoproliferative syndrome (XLP, Duncan's disease)
- Studies of the gene defective in the Wiskott-Aldrich syndrome (WAS)
- Studies of host defense molecule polymorphisms in the Wiskott-Aldrich syndrome (WAS)
- The search for a gene responsible for common variable immunodeficiency (CVID) and selective IgA deficiency using cDNA microarrays
- Treatment of patients with X-linked hyper IgM syndrome (XHIM) with recombinant CD40 ligand (CD40L)
- Treatment of selective IgA deficient patients with recombinant B-lymphocyte stimulator (BLyS)

Item

Prostate cancer -- Incidences of prostate cancer have been on the rise in recent decades. Evidence is growing that in addition to genetic disposition, numerous other factors--including

lifestyle, nutritional imbalances, chronic infections, and hormonal, psychological and environmental components--play a role in the development of prostate cancer. The Committee strongly urges the NIH to renew its commitment to prostate cancer research, with a special emphasis on accelerating new avenues for basic research, drug development, and clinical research. (p. 103)

Action taken or to be taken

Prostate cancer is the most common type of cancer in men with the exception of skin cancers. In 2001, an estimated 198,100 men were diagnosed with the disease, and 31,500 died from it. No other cancer rises in both incidence and mortality with increasing age as rapidly as prostate cancer. As the U.S. population ages, the impact of this cancer will increase. Furthermore, certain segments of the population are disproportionately affected. For example, African American men are far more likely to develop prostate cancer and twice as likely to die from it than are other Americans. Although significant progress has been made over the past several years to improve our understanding of prostate cancer, there is still much to learn about its causes, early detection, diagnosis, treatment, and prevention.

The NCI has prepared a prostate cancer research plan that will enable NCI and other NIH Institutes and Centers to respond to discoveries and opportunities while ensuring the best use of resources and a smooth flow between advances in knowledge and application. The plan outlines goals, objectives, and near-term milestones in seven different scientific areas that span the continuum of research: 1) Biology, Progression and Metastasis; 2) Etiology and Prevention; 3) Early Detection, Diagnosis, and Prognosis; 4) Treatment; 5) Cancer Control, Survivorship, and Outcomes; 6) Laboratory and Preclinical Models; 7) Resources and Capacity Building. In focusing on these areas, it is critical that we:

- Elucidate the molecular and cellular processes that lead to prostate cancer initiation, progression, and metastasis.
- Discover genetic, biochemical, environmental, and lifestyle factors and their interactions that define prostate cancer risk, play causal roles in prostate cancer initiation and progression, and inform the development of new strategies for prevention and early detection.
- Use knowledge gained about the molecular and cellular biology of prostate cancer to develop improved methods for detecting and diagnosing pre-malignant and malignant lesions and for better predicting disease progression and response to therapy.
- Accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer.
- Achieve a continuously improved understanding of the impact of prostate cancer and its care on individuals, families, and populations with special emphasis on survivorship, improving quality of care, and steadily reducing disparities in both care and outcomes.
- Develop and validate accurate prostate cancer models and ensure that they are integrated into research on the biology, prevention, early detection and treatment of prostate cancer.
- Maximize the effectiveness and efficiency of prostate cancer scientists by providing them with essential resources and infrastructure for conducting their research.

Biology, Progression, and Metastasis

Over the past decade, significant progress in characterizing the molecular and cellular changes that underlie prostate cancer has been made. The intracellular mechanisms responsible for malignant transformation and cancer progression, as well as the interactions between the cancer cell and its environment that influence organ invasion, metastases, hormone-independent growth, and resistance to cell death are being defined. These findings raise hope for improvement in the prevention, diagnosis, treatment, and control of prostate cancer.

Recent Advances in Research

Abnormalities on Chromosomes 8 and 10 May Be Associated with Prostate Cancer Development. NCI-supported researchers identified a mutation on chromosome 8 (8p21) in the tumors of approximately 80 percent of prostate cancer patients studied. This region overlaps a region that was identified as a locus for familial breast cancer. Deletions were also found in 63 percent of precancerous prostate lesions, suggesting that abnormalities on 8p21 may be associated with early stages of prostate cancer development. A map of this region is being constructed, and researchers have begun analyzing candidate genes that reside in this area.

Candidate Tumor Suppressor Genes Identified. In other NCI funded research, investigators are identifying new candidate tumor suppressor genes for study. One group of NCI-funded researchers used a combination of *in vitro* techniques and genetic database searches to determine that the gene *LZTS1* on chromosome 8 (8p22) is involved in the regulation of cell growth and may be a prostate tumor suppressor gene. Another group showed that the gene *KLF6*, located on chromosome 10p, is mutated in a subset of prostate cancer tumors, but not in normal prostate tissue from the same individuals. Their data suggest that *KLF6* is a tumor suppressor gene involved in human prostate cancer.

Osteoclasts Play an Important Role in Bone Metastasis of Prostate Cancer. Scientists have long known about the role of osteoblasts – cells that are the normal precursors to bone formation – in bone metastasis. Recently the extensive, but little understood role of osteoclasts, cells that are normally involved in the breakdown of bone, were discovered. To examine the contribution of osteoclasts to bone metastasis, NCI-funded researchers injected human prostate cancer cells both beneath the skin and into a leg bone of mice. Tumors easily grew at both injection sites when osteoclast activity was normal. When researchers used a drug called osteoprotegerin to block osteoclast activity at the same time as injecting the cancer cells, subcutaneous tumors would still grow, but tumor growth in the tibia was prevented. The results suggest that osteoclast activity is integrally involved in the establishment of prostate metastasis in bone and that inhibition of osteoclast activity may prevent or slow this growth.

Etiology and Prevention

Significant strides in detecting, diagnosing, and treating prostate cancer have been made, but a fuller understanding of the genetic, biochemical, and environmental risk factors that contribute to its development and progression is key to effective prevention. Increasing our understanding of

causes is essential to the development of effective prevention methods. Currently, limited knowledge hinders prevention efforts and underscores the need to more fully identify these variables and determine how they interact to modify risk. Further research is also needed to determine what causes some prostate cancers to become particularly aggressive while others remain relatively harmless. Identifying risk factors and determining how they contribute not only to onset of the disease but also to progression will provide the foundation for effective prevention strategies.

Recent Advances in Research

Large Study Shows Positive Effects of Vitamin E in Preventing Prostate Cancer. A large cancer prevention trial conducted by the NCI in collaboration with the National Public Health Institute of Finland showed that daily use of a modest-dose Vitamin E supplement led to a striking reduction in prostate cancer incidence. These promising results have enormous public health implications in that they describe the first time a simple, practical intervention has been shown to protect against the most common cancer in American men. How Vitamin E works to prevent prostate cancer is the focus of ongoing research, such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT), and may also have relevance to other cancers.

Researchers Identify Specific Gene Associated with Prostate Cancer in Some Families. Researchers from a consortium of 14 institutions, including the National Human Genome Research Institute (NHGRI) and investigators supported by the NCI, have found mutations that inactivate the RNASEL gene in some families with a history of prostate cancer. RNASEL is a gene that plays a role in defending cells from viruses and assists in normal cell turnover or programmed cell death. Inactivating this cellular self-destruct mechanism through genetic mutation may help scientists understand why some prostate cells become cancerous. This new discovery provides further proof that hereditary factors play a major role in prostate cancer risk. Investigators continue to aim at identifying all of the common contributing genes to hereditary susceptibility.

Genetic Mutation May Explain Higher Rates of Prostate Cancer in Certain Populations. NCI-supported researchers have identified a genetic mutation that may provide clues to the causes of prostate cancer and help to explain the much higher rates of prostate cancer among African American and Hispanic American men as compared to Caucasians. Because prostate cancer is known to "feed off" male hormones, this research team studied a gene for the enzyme steroid 5-alpha-reductase – that controls aspects of hormone metabolism. They identified a simple mutation on the *SRD5A2* gene that occurs rarely in most healthy African American and Hispanic American men, but much more frequently in those who have prostate cancer. The more advanced the cancer, the more often this mutation seems to be present. This intriguing finding requires further evaluation and confirmation, but it identifies a potential prostate cancer related gene that may be especially important for specific racial or ethnic groups.

Early Detection, Diagnosis, and Prognosis

Current prostate cancer screening and early detection results pose serious dilemmas for men and their health care providers. This is because many more prostate cancers are present in men over age 50 than ever become clinically apparent or significant. Although early detection, primarily through PSA screening, may have decreased prostate cancer mortality, the test does not differentiate between tumors that will lead to fatal disease and those that will remain clinically insignificant. In the recent American Society of Clinical Oncologists (ASCO) meeting new research was presented that might lead to changes in the clinical practice as related to monitoring person's PSA levels. Expanding our understanding of prostate cancer biology will allow for the development of diagnostic tools and the identification of new targets for prevention, early diagnosis, and treatment, while new technologies will provide improved means of identifying diagnostic markers.

Recent Scientific Advances

Serum Proteomic Patterns for the Detection of Prostate Cancer. Pathologic states within the prostate may be reflected by changes in serum proteomic patterns. A recent study published in the Journal of the National Cancer Institute described the use of proteomic profiling in serum to discriminate men with benign disease from those with prostate cancer: specfically when the men have a marginally elevated PSA (4-10 ng/mL). If validated in future series, serum proteomic pattern diagnostics may be of value in the decision to biopsy men with an elevated PSA. This test could prevent suffering and defray significant health care costs by assisting the urologist in the decision to biopsy or to watch and wait.

Thymosin beta 15 may be a new prognostic marker. A newly discovered protein, thymosin beta 15, that stimulates cell motility and invasion of surrounding tissues has been found to be present in much higher amounts in prostate cancer cells and in those patients who fail therapy. Thymosin beta 15 is currently being tested in a clinical trial as a potential prognostic test for prostate cancer.

PSA levels in White and African American men are similar. In an effort to understand why prostate cancer rates are higher in African Americans than in other American men, researchers measured PSA levels in the blood of African American and White American men. PSA levels were found to be comparable and therefore do not explain the disparity.

New PSA Monitoring Guidelines. In the recent American Society of Clinical Oncologists new research was presented suggesting annual screening of men with PSA between 2-4. Screening once every five years was suggested for those with PSA of 1 or less.

New information on the value and use of PSA screening. Findings from the Baltimore Longitudinal Study of Aging have provided several insights into the value and use of Prostate Serum Antigen (PSA) screening, including data on levels of risk related to age, PSA level, and rates of change in PSA level. Investigators have discovered that free PSA (PSA in the blood not bound to proteins) is predictive of the aggressiveness of prostate cancers. By tracking changes in

PSA levels, detection of prostate cancer was possible up to 10 years before it could be diagnosed by other means. Furthermore, current work is showing that normal levels of PSA can be stratified to identify men at high risk of developing prostate cancer over a 20 to 30 year period.

Two new imaging agents for detecting prostate cancer are under study. One new imaging agent for detecting prostate cancer is a contrast agent that enhances positron emission tomography (PET). The second is a probe that can improve the accuracy with which magnetic resonance imaging can detect the earliest stages of angiogenesis accompanying tumor development.

Magnetic Resonance Spectroscopy Imaging (MRI). MRI will be tested in a multi-institutional clinical trial to determine its value in identifying active tumors in the prostate following positive screening tests.

Treatment

Although genuine options are available for curing prostate cancer when it is localized, these are not reliable ways to predict the behavior of an individual cancer, nor how to predict whether an individual cancer will respond well to one particular treatment compared to another. Moreover, while treatments for localized prostate cancer usually are effective, they are not *always* effective, nor are they free from troublesome side effects. Further development of optimal treatments for the continuum from early stage disease to advanced lethal prostate cancer is needed.

Recent Scientific Advances

New Drugs Provide Hope for Prostate Cancer Patients with Bone Metastases. When prostate cancer spreads, it often invades the bones, where it causes severe, debilitating pain. However, several drugs currently under study may combat bone metastases, slowing the spread of the cancer and improving the patient's quality of life. Clodronate, a bisphosphonate, has shown activity against prostate cancer metastasis, opening the door for further studies involving more potent bisphosphonates, or higher doses of the drug. A second drug, Atrasentan, targets the protein endothelin-1, which promotes cell growth in bone and which is overactive in prostate cancer cells.

Radiation Plus Hormone Treatments Extend Lives of Prostate Cancer Patients. NCI-supported investigators conducted a randomized clinical trial in which men who had been treated with surgery for early-stage prostate cancer were assigned either to receive immediate hormonal therapy or to simply be observed until their disease progressed. All of the men had microscopic tumor metastases in their lymph nodes (node positive), putting them at high risk for recurrence of their cancer. The results of this trial, together with evidence from previous studies, support the hypothesis that early hormonal therapy may prolong survival. The trial has changed the standard of care for node-positive prostate cancer patients, and the dramatic results also suggest that early administration of hormonal therapy could extend the lives of many other prostate cancer patients.

Translational Research Promises to Yield New Targets for Treating Prostate Cancer. At this time, our knowledge of exploitable targets for prostate cancer is still developing. NCI is currently funding a number of projects to enhance this knowledge by examining targets in prostate cancer cell lines. These studies may help scientists find ways to block cancer metastasis, suppress the growth of cancer cells by interfering with nuclear proteins, and block tumor growth by controlling expression of certain genes.

Cancer Control, Survivorship and Outcomes

New approaches to early detection as well as improvements in treatment have resulted in a dramatic rise in the long-term survival rate of prostate cancer patients. Most patients can now expect to live more than 10 years after diagnosis. However, the same treatments that have enabled long-term survival can also cause potentially disabling effects ranging from minor alterations in day-to-day activities to major functional loss involving critical organs. Furthermore, the true effect on mortality from specific screening and treatment measures remains uncertain. Therefore, more data about all aspects of treatment outcome and quality of life are needed to provide a more comprehensive and complete perspective on the needs of the long-term cancer survivor. Increased surveillance of the early detection, treatment, and outcomes of prostate cancer in the population are required. Better qualitative and quantitative measures of the risk factors, use of interventions, cost of treatment, and quality of life among prostate cancer patients and survivors are crucial. Major efforts are still needed to stimulate research on prostate cancer survivorship.

Recent Scientific Advances

The Prostate Cancer Outcomes Study. This ongoing study is enabling comparisons of treatment modalities in various combinations in terms of their success medically and on quality of life, and has produced more than a dozen of peer-reviewed publications along with citations throughout much of the prostate cancer outcomes literature.

Estimates of Long-term Treatment Complications Are Higher Than from Previous Studies. 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% versus 62%), although large, statistically significant declines in sexual function were observed in both treatment groups.

Diagnosis of Prostate Cancer is Similar in Different Health Care Settings. In one study comparing treatment and outcomes among Medicare recipients in HMOs and FFS settings, researchers looked at the same geographic area and found that 10-year survival following a diagnosis of non-metastatic prostate cancer was similar for men treated in each setting, although there were significant differences in treatment between the FFS and one of the HMOs.

The Races Differ in Their Use of Prostate Cancer Treatment. Despite the increased use of aggressive treatment overall, only 17.2 percent of black men received radical prostatectomies versus 27.7 percent of white men while 49.0 percent of black men had conservative therapy versus 38.1 percent of white men.

Study of Cancer Survival Rates in Underserved Populations. Research is demonstrating that differences in cancer morbidity and mortality previously attributed to race are not due to supposed biological differences between populations or between the tumors individuals develop.

Laboratory and Preclinical Models

In its quest to rapidly advance prostate cancer research, NCI is committed to developing more accurate models of prostate cancer. Prostate cancer researchers will use these models to screen drug candidates, conduct preclinical studies of new drugs, and better understand the biology of human prostate cancer. Currently, multiple models are available to the scientific community such as xenograft, cell lines, transgenic, reconstitution, spontaneous tumor, and hormonally induced models. However, limitations within each of these model systems have prompted NCI to support the development of additional models that more faithfully imitate the human disease. NCI's strategic plan to develop more accurate prostate cancer models focus on five major areas: 1) mouse models, 2) models in other species, 3) transplantation technologies in model development, 4) models for studying prostate epithelium and underlying stroma, and 5) computational and in-silico mathematical models of prostate cancer.

Advances in Research

Researchers use mouse models in which certain genes have been altered or inactivated to advance studies on several aspects of prostate cancer.

- The normally functioning *PTEN* gene – whose mutated form is found in a large percentage of prostate and other cancers – plays a critical role in regulating cell growth and specialization and acts as a tumor suppressor gene. Researchers are using mouse models to study how and when the loss of PTEN protein function fits into the chain of genetic mutations that can lead to tumor development. One research group has designated a mouse model that lacks PTEN and another important protein, p27. These mice develop spontaneous tumors in the prostate and other organs.
- A mouse model that carries a defect known as the "*TRAMP* transgene" permits investigators to analyze sequential genetic changes that occur during the multi-step process in prostate carcinogenesis. Researchers use this model to study hormone-independent tumor growth, which occurs in humans with the failure of androgen-ablation therapy. The model has been used in several chemoprevention and chemotherapy studies.

Xenografts model the late stages of prostate cancer progression. A model has been developed to study tumors that stop responding to androgen ablation therapy. For this model, investigators first isolated a special cell line from a patient with advanced prostate cancer. When some of these cells are transferred to the prostate of mice, they metastasize to a number of organs,

including the lymph nodes and skeleton. The pattern of metastasis is similar to that seen in human prostate cancer.

Research using micro-PET is expected to reveal new avenues for human therapy. Scientists involved in developing mouse models for prostate cancer have teamed with colleagues from the NCI-funded Small Animal Imaging Resource Program to use positron emission tomography (micro-PET, when it is used on mice) to study prostate cancer development, from its beginnings in the prostate to its metastasis (spread) to bone and other organs.

Resource and Capacity Building

The infrastructure for tissue acquisition, storage and use; data sharing across disciplines; and information sharing to link the efforts of various initiatives and programs are challenges to prostate cancer research. The scientific community has witnessed an incredible surge in the development of new biomedical technologies, and in the next few years, tissue-based and bioinformatics systems for prostate cancer research will expand greatly. NCI has played a critical role in developing and applying a wide variety of novel technologies, but there is room for improvement in the dissemination and application of such new technologies for prostate cancer research.

Ongoing Initiatives That Support Resource and Capacity Building

NCI has expanded the **Prostate Cancer Specialized Programs of Research Excellence** (SPOREs) for translational research, from four funded Prostate Cancer SPOREs in 2000 to nine SPOREs in 2003. The programs provide valuable infrastructure for translational research to develop new scientific approaches in early detection, diagnosis, treatment, and prognosis of human prostate cancer. An expanded network of prostate SPOREs is scheduled to bring about Inter-SPORE scientific studies that will conduct innovative pilot and early phase clinical interventions.

The NCI **Tissue Expediter** provides information on sources of human tissue specimens and helps prostate cancer and other researchers locate the tissue and related data they need. The tissue expediter is a scientist with contacts in the resources community who can rapidly relate investigator needs to appropriate resources. The **Specimen Resource Locator** is an invaluable database with query tools to help prostate cancer researchers locate resources such as tissue banks and tissue procurement services with access to normal, benign, pre-cancerous and/or cancerous human tissue.

The **Cancer Genome Anatomy Project** (CGAP) is a multi-initiative NCI program to build a complete profile of genes expressed in normal, precancerous, and cancer cells and help cancer researchers elucidate major steps of tumor development, develop molecular diagnostic techniques, and identify molecules that can be used for early detection or drug discovery. Researchers throughout the world have started mining CGAP databases to identify molecular signatures of prostate and other cancers and are discovering new potentially cancer-causing

genes, identifying candidates for molecular targets research, and helping to build microarrays for cancer cell signature research.

A **new national system for Cancer Clinical Trials** involves a fundamental change in how NCI develops, reviews, conducts, and supports prostate and other cancer clinical trials. The overall goal of the new system is to accelerate the pace of all clinical research to more rapidly answer important research questions. The revitalized system is more flexible and promises to speed new ideas from lab to clinic, increase physician and patient participation, and streamline administration and data reporting.

NCI is building **Minority Institution/Cancer Center Partnerships** to link Minority-Serving Institutions with NCI Cancer Centers to increase the number of minority students engaged in prostate and other cancer research; strengthen the research capabilities of minority institutions; and reduce incidence and mortality in minority populations. NCI has also collaborated with Minority-Serving Institutions to increase access to and involvement in clinical trials by underrepresented populations, minority researchers, and patients and physicians. These efforts are especially critical for prostate cancer because of the high incidence and mortality rates among certain minority populations.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2003 Amount Authorized	2003 Amended President's Budget	2004 Amount Authorized	2004 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Cancer Institute	Section 41B	42§285b	Indefinite	$4,535,696,000	Indefinite	$4,695,471,000
National Research Service Awards	Section 487(d)	42§288	a/	73,289,000	b/	75,048,000
Total, Budget Authority				4,608,985,000		4,770,519,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
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				(9,172,000)
2003	4,673,510,000			
2004	4,770,519,000			

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 reductions 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 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
Office of the Director	735	751	739
Center for Cancer Research	1,574	1,610	1,586
Division of Cancer Biology	51	59	58
Division of Extramural Activities	110	115	113
Division of Cancer Treatment and Diagnosis	206	212	208
Division of Cancer Prevention	98	101	99
Division of Cancer Control and Population Sciences	143	148	145
Division of Cancer Epidemiology and Genetics	140	145	142
Total	3,057	3,141	3,090
FTEs supported by funds from Cooperative Research and Development Agreements	(3)	(3)	(3)

FISCAL YEAR	Average GM/GS Grade
2000	11.2
2001	11.3
2002	11.4
2003	11.4
2004	11.4

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Detail of Positions

GRADE	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
ES-6	1	1	1
ES-5	4	4	4
ES-4	3	3	3
ES-3	0	0	0
ES-2	1	1	1
ES-1	0	0	0
Subtotal	9	9	9
Total - ES Salary	$1,237,481	$1,278,009	$1,307,083
GM/GS-15	249	251	249
GM/GS-14	323	326	323
GM/GS-13	288	291	289
GS-12	453	458	454
GS-11	266	270	268
GS-10	28	28	28
GS-9	186	188	186
GS-8	157	158	157
GS-7	162	164	163
GS-6	34	34	34
GS-5	31	31	31
GS-4	17	17	17
GS-3	9	9	9
GS-2	1	1	1
GS-1	1	1	1
Subtotal	2,205	2,227	2,210
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	53	53	53
Senior Grade	22	22	22
Full Grade	11	11	11
Senior Assistant Grade	2	2	2
Assistant Grade	0	0	0
Subtotal	89	89	89
Ungraded	865	873	866
Total permanent positions	2,189	2,210	2,193
Total positions, end of year	3,168	3,198	3,174
Total full-time equivalent (FTE) employment,end of year	3,057	3,141	3,090
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$137,498	$142,001	$145,232
Average GM/GS grade	11.4	11.4	11.4
Average GM/GS salary	$66,765	$68,911	$70,479