DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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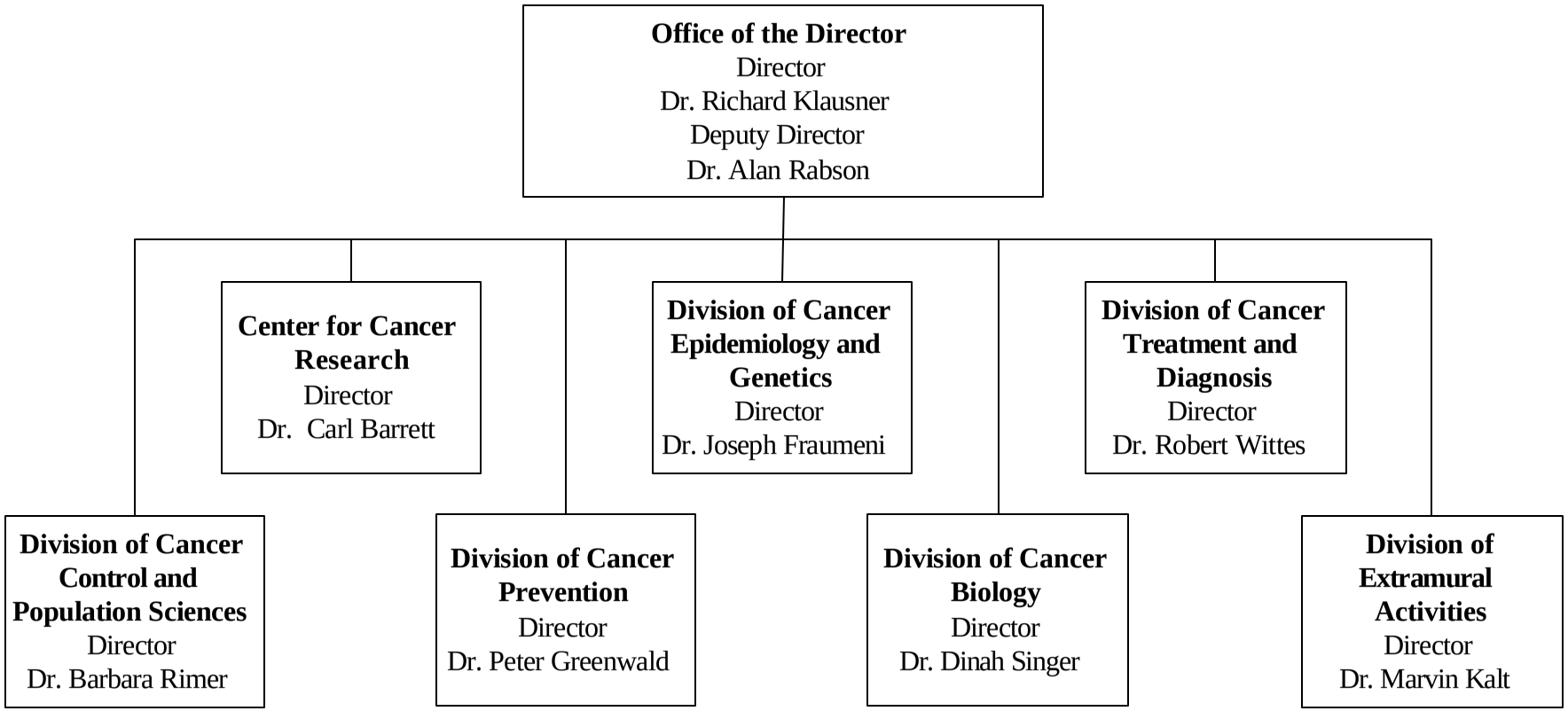
Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer, [$3,757,242,000] *$4,177,203,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated and Emergency Supplemental Appropriations Act for Fiscal Year 2001 (P. L. 106-554)]

National Institutes of Health

National Cancer Institute

Amounts Available for Obligation 1/

Source of Funding	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Appropriation	$3,332,317,000	$3,757,242,000	$4,177,203,000
Enacted Rescission	(17,763,000)	(2,005,000)	---
Subtotal, Adjusted Appropriation	3,314,554,000	3,755,237,000	4,177,203,000
Real transfer to:			
Other NIH Institutes through the NIH Director's one-percent transfer authority	(2,778,000)	---	---
Other HHS Agencies through Secretary's one-percent transfer authority	(695,000)	---	---
Real transfer to HHS for the Office of Human Research Protection	(0)	(781,000)	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	1,577,000	1,643,000	
Comparative transfer to:			
Other NIH Institutes as a result of a change in assessment formula for Central Services funding	(2,867,000)		
National Institute of Allergy and Infectious Diseases for the Vaccine Research Laboratory	(13,671,000)	(18,171,000)	
Subtotal	3,296,120,000	3,737,928,000	4,177,203,000
Unobligated Balance, start of year 2/	4,150,000	---	---
Revenue from Breast Cancer Stamp 2/	3,101,000	---	---
Unobligated Balance, end of year 2/	(3,753,000)	---	---
Subtotal, adjusted budget authority	3,299,618,000	3,737,928,000	4,177,203,000
Unobligated balance lapsing	(0)	---	---
Total obligations	3,299,618,000	3,737,928,000	4,177,203,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2000 - $15,932,100 FY 2001 - $20,000,000 FY 2002 - $22,360,000
Excludes $36,147,381 in FY 2000 and $26,700,000 in FY 2001 for royalties.

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

JUSTIFICATION

NATIONAL CANCER INSTITUTE

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

Budget Authority:

FY2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase of Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2,794	$3,299,618,000	3,150	$3,737,928,000	3,245	$4,177,203,000	95	$439,275,000

This document provides justification for the Fiscal Year 2002 activities of the National Cancer Institute (NCI), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

As the 21st century dawns, scientific discovery is occurring at a pace that would astound our forebears. Nearly every day some new advance or insight brings us closer to answering one of the many questions that have long confounded scientists, and nowhere is the excitement more evident than in cancer research. Our pace of discovery is fueled by progress in the explosion of information on the fundamental nature of cancer, the development of new tools and approaches for conducting clinical research to test these insights in patients, and the growing sophistication in behavioral and population research that allows us to understand and address the burden of cancer.

We are encouraged by evidence that progress in our understanding of cancer and our ability to detect and treat it contributed to a decline in the rates of new cancer and overall deaths from cancer in the United States between 1990 and 1997.[1] For the first time, between 1996 and 1997, the annual number of cancer deaths did not rise, despite a growing and aging population. And death rates for the four most common cancer sites – lung, colorectal, breast, and prostate – continue to drop, albeit slowly.

Our excitement is tempered, however, by the knowledge that far too many Americans continue to suffer and die from cancer each day. Death rates are still rising for several cancers, including non-Hodgkin's

[1] *Annual Report to the Nation on the Status of Cancer, 1973-1997*, prepared jointly by the National Cancer Institute, the American Cancer Society, the National Center for Health Statistics/Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries.

lymphoma, multiple myeloma, and liver, kidney, and esophageal cancers. Declines in the incidence of cancer stemming from dramatic reductions in adult tobacco use may stall – or even reverse – if teen smoking continues at current levels. Moreover, the overall number of Americans who develop cancer is expected to increase as our population ages and "baby boomers" enter the time of life when cancer is most common. And not all groups of people are benefiting equally from our advances against cancer. Rates of colon cancer, for instance, are declining overall, but not among African Americans.

Too many Americans, for a host of reasons, lack access to high quality, cutting-edge cancer treatment and care. An increase in the number of people with cancer will, in turn, place mounting pressure on our Nation's capacity to respond. With the expected growth and aging of the U.S. Population, the costs of cancer treatment are predicted to nearly double over the next decade, rising to just under $100 billion. The costs of screening more people will add another five to ten percent to this bill. Keenly felt, but less easily calculated, are the productivity and contributions lost to society when people are afflicted with cancer.

NCI's proposed activities for Fiscal Year 2002 will support continued cutting edge cancer research as well as substantial investments in the essential building blocks of medical research: the training and career development of investigators, scientific tools and information resources, and collaborative research environments that foster the exchange of information and speed the progress of research. NCI will also continue efforts to improve the transfer of research results into practice, research and enhance the quality of cancer care, and investigate and reduce disparities in the incidence and treatment of cancer.

The justification for our activities is straightforward. We have advanced significantly in numerous areas of endeavors scientific advances that in turn provide opportunity for continued discovery in numerous areas. We have the structures in place to take advantage of these opportunities but need to continue maintaining and building them. Most importantly, we still have a lot of work to do. We have the systems in place, good people standing ready to do it, and extraordinary opportunities to build upon past discovery that will help us achieve our goal to "stimulate and support research and its application – to achieve a future when all cancers are uncommon and easily treated."

SCIENCE ADVANCES

Through advances in our understanding of cancer at the molecular level, we are witnessing and facilitating a fundamental change in the way scientific discovery is accomplished. Using a more "designed" research approach, we identify a range of compelling options for prevention, detection, diagnosis, and treatment; verify their efficacy using models and electronic tools; and validate them through extensive testing and clinical trials. Increasingly, cancer research brings together and melds different scientific perspectives and the tools of multiple disciplines. By integrating the work of epidemiologists, geneticists, and population scientists, we hope to better understand the potential interplay among inherited susceptibility, lifestyle, and exposure to environmental pollutants and infectious agents in cancer causation. As the depth of our knowledge of cancer grows, we will be able to bring the benefits of increasingly sophisticated scientific discovery to the American people more quickly.

New Approaches to Pathogenesis

Powerful Tool Reveals Most Common Non-Hodgkin's Lymphoma Is Actually Two Diseases
Lymphomas, which include Hodgkin's disease and non-Hodgkin's lymphoma (NHL), are the fifth most common type of cancer diagnosed and the sixth most common cause of cancer-related death in the United States. Non-Hodgkin's lymphoma is the more common of the two basic lymphoma types. This disease – often painless in its early stages – may occur in a single lymph node, a group of lymph nodes, or in another organ, and can spread to almost any part of the body, including the liver, bone marrow, and spleen. The most common type of non-Hodgkin's lymphoma is an aggressive cancer called diffuse large B-cell lymphoma (DLBCL). Forty percent of patients with a diagnosis of DLBCL are cured by standard multi-agent chemotherapy. However, a compelling 60 percent of DLBCL patients fail to respond to chemotherapy.

NCI-supported scientists now have been able to use a novel microarray tool, which they have labeled the "lymphochip" to gain insight into this problem. By mining the Cancer Genome Anatomy Project (CGAP) database for more than 18,000 genes important to both lymphoid malignancies and the immune system and placing them on a device similar to a computer chip, the researchers were able to compare gene activity of normal and cancerous B cells and to generate gene expression profiles, or "signatures," of the different cell types. After examining several different forms of non-Hodgkin's lymphoma, the scientists discovered that DLBCL showed two distinct patterns of gene expression, suggesting that this diagnosis has lumped together *two* subtypes of NHL. While unable to distinguish one from the other under a microscope, the tool conventionally used for diagnosis and cell typing, scientists now are able to use advanced technology to sort out these two biologically distinct subtypes of lymphoma and to subsequently identify two distinct clinical courses that DLBCL can take.

Although more research is needed, scientists are optimistic that expression signatures will lead them to more precise diagnoses and ultimately to more effective treatments for specific subtypes of this disease. This study points the way to a future when physicians may be able to diagnose and treat cancer based on well-characterized biological differences among tumor cells, more accurately predict how aggressive a tumor will be, and utilize new and possibly more effective therapies tailored to the characteristics of an individual's disease.

Estrogen Replacement Therapy and Breast Cancer Risk
The favorable effects of estrogen replacement therapy (ERT) on the heart (protection against coronary heart disease), bone (protection from osteoporosis), and quality of life (effective relief from menopausal symptoms) have made this treatment a desirable option for the majority of menopausal women. And, some studies have also suggested that a combination of estrogen and progestin may make hormone replacement therapy less of a risk for certain types of cancer.

However, a team of NCI-supported researchers has found that women who use combined estrogen-progestin replacement therapy have a greater risk for developing breast cancer than those who use estrogen alone. Using 15 years of follow-up data from 46,000 women who participated in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program, the scientists

found that, compared to non-users, the relative risk for breast cancer increased by eight percent per year for estrogen-progestin therapy compared to one percent for estrogen therapy alone in women who had used hormones during the previous four years. Both groups had a higher risk than non-users. Short-term use (two to three years) was not associated with increased risk, suggesting that women who take menopausal hormones for shorter periods are not at increased risk of breast cancer.

The increase in risk is still low for women taking both hormones, but this and other studies do suggest that women need to consider the possible risks and uncertainties associated with hormone replacement therapy, despite reported beneficial effects on the bones, the heart, and quality of life.

New Preventive Strategies against Disease

Daily Smoking Is Not Necessary for Nicotine Dependence in Young People
More than 3 million adolescents in the United States smoke, and every day another 6,000 young people begin smoking. While cigarette smoking has been declining among American adults, the number of adolescents who smoke has risen sharply since 1992. Like adult smokers, adolescents report frequent unsuccessful attempts to quit, and they cite withdrawal symptoms and the "urge to smoke" among the reasons why they find it difficult to give up smoking. However, because many young people have not yet become daily smokers, researchers have tended not to regard them as nicotine dependent. The traditional model for the development of nicotine dependence is progression from experimental tobacco use to occasional use, then to daily use that increases in frequency, resulting in dependence.

Recently, however, NCI-supported researchers found evidence of nicotine dependence and withdrawal among young tobacco smokers *before* they become daily smokers. They found that 63 percent of a group of 7th-grade students (ages 12-13) who smoked one or more cigarettes a month reported experiencing one or more symptoms of nicotine dependence. These symptoms included cravings, withdrawal symptoms (depressed mood, irritability, anger, anxiety, difficulty concentrating, and restlessness) and loss of control over the amount and duration of tobacco use. More than one in five of these students reported symptoms of nicotine dependence within 4 weeks of beginning to smoke with 20-68 percent of adolescent smokers being classified as dependent. And about two-thirds reported experiencing withdrawal symptoms when they cut down or tried to quit smoking.

This finding points to the importance of preventing young people from starting to smoke, the value of intervening early to help young smokers quit, and the need to develop new assessment instruments for studying tobacco use in young people.

Several Factors Predict Smoking Cessation in Adolescents
In a follow-up study to determine their tobacco quitting behaviors, 15.6 percent of adolescents who participated in a 1989 survey of smokers aged 12-19 years were found to have quit during the four years following the original survey. "Smokers" were defined as those who had smoked more than 100 cigarettes in their lifetime and had smoked at least one cigarette during the 30 days before the 1989 survey.

Researchers identified factors that predict quitting among adolescent smokers and discovered that adolescents were significantly more likely to quit smoking when: (1) they were occasional, rather than daily, smokers; (2) they had never quit smoking or had previously quit for 14 days or more; (3) their mothers did not smoke; (4) they assumed they would not be smoking 1 year later; and (5) they had few symptoms of depression.

These findings have important implications for treatment and cessation programs for adolescent smokers. Nicotine dependence is only one factor in predicting success at quitting. Other variables include the emotional state of the smoker, depression, and environmental factors such as a mother who smokes. All these need to be taken into account when developing adolescent smoking cessation programs. The data also provide additional support for the role of depression in smoking behavior.

Weighing the Risks and Benefits of Tamoxifen in Breast Cancer Prevention
In response to findings from the Breast Cancer Prevention Trial that tamoxifen treatment produced a 49 percent reduction in the risk of invasive breast cancer in a population of women at elevated risk, the National Cancer Institute sponsored a workshop to study and develop information tools to assist in counseling and in weighing the risks and benefits of tamoxifen.

Scientists reviewed information on the incidence of invasive breast cancer and of *in situ* lesions as well as on several other health outcomes in the absence of tamoxifen treatment. They then reviewed data on the effects of tamoxifen on these outcomes and developed methods to compare the risks and benefits of tamoxifen. They found that the risks and benefits of tamoxifen depend on age and race as well as on a woman's specific risk factors for breast cancer. In particular, the absolute risks from tamoxifen of endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis increase with age. These absolute risks differ between white and black women, as does the protective effect of tamoxifen on fractures. The primary conclusion from this study was that tamoxifen is most beneficial for younger women with an elevated risk of breast cancer. The researchers developed tables and aids for use by health care providers and women in weighing the risks and benefits of using tamoxifen to reduce breast cancer risk.

New Avenues for the Development of Therapeutics

Novel Bone Marrow Transplant Offers New Hope to Patients with Cancers of the Blood
Bone marrow transplants are an effective treatment for patients with cancers of the blood: leukemia, multiple myeloma, and non-Hodgkin's lymphoma. The bone marrow is where most hematopoietic stem cells – immature cells from which all blood cells develop – are found. A bone marrow treatment involves destroying the patient's diseased bone marrow with high doses of chemotherapy or radiation and replacing it with healthy marrow from a matched donor. Conventional bone marrow transplants are not normally performed on patients older than 55 or on patients who are unfit to withstand the intensive, highly toxic treatment regimen. Thus, this potentially curable treatment is currently available only to the minority of patients with cancers of the blood who are under 55 and in good physical condition.

NCI-supported researchers have developed an experimental bone marrow transplant procedure known

as a “mini-transplant.” Instead of using high doses of radiation to kill cancer cells, this procedure takes advantage of the immune properties of donor stem cells. In a process called the “graft versus tumor” effect, the donor cells recognize and kill cancer cells while tolerating the patient's normal cells and tissues. The mini-transplant requires a much lower dose of radiation than a conventional bone marrow transplant – just enough to suppress the patient's immune system without wiping out the bone marrow. The procedure has been performed on over 80 patients whose average age was 56. Patients did not experience hair loss, severe mouth sores, low levels of blood cells, and other adverse effects that frequently occur in patients receiving conventional transplants. Five patients (six percent) died within the first year; this compares with a mortality rate of 25 percent for younger patients with chronic myeloid leukemia who underwent conventional transplants. Most mini-transplant patients went home from the hospital the same day. By contrast, recipients of conventional transplants are hospitalized in intensive care for 2 to 3 months. Rates of graft-versus-host disease, in which the transplanted tissue mounts an immune attack on the patient's cells, were similar to those that occur after conventional transplants.

If shown to be effective in Phase III clinical trials, the mini-transplant procedure will make bone marrow transplants more available, less toxic, less costly, and more effective. The procedure may also be effective in treating solid tumors as well as autoimmune diseases, genetic diseases, and sickle cell anemia.

Applying Laboratory Research to Develop a Therapy for Chronic Myelogenous Leukemia
Understanding the molecular mechanisms that contribute to chronic myelogenous leukemia (CML), a form of leukemia that affects white blood cells or granulocytes as they form in the bone marrow, has led to a promising, targeted new treatment for this disease. For some time, scientists have known that the Philadelphia (Ph) chromosome, which causes the production of the tyrosine kinase enzyme, is unique to tumor cells and that nearly all patients with CML carry the genetic mutation that gives rise to it. But it was just recently that NCI-supported scientists discovered the underlying mechanism by which CML arises and progresses. The researchers were able to show that leukemia cells in nearly all CML patients express an abnormal protein known as Bcr-Abl and that this aberrant protein alone is enough to cause CML. The researchers also established that the tyrosine kinase activity produced by the Bcr-Abl protein is required for the disease to progress.

The researchers were then able to use this information to determine that a new drug known as STI571, developed by Novartis Pharmaceuticals, provided an opportunity to test their hypothesis that targeting cells that express Bcr-Abl might halt or slow CML. In cell culture and animal studies, STI571 specifically targeted Bcr-Abl expressing leukemia cells with no obvious effect on normal cells. In studies of human patients, the researchers found that all patients with chronic-phase CML who were treated with STI571 had complete remission. Several patients even showed a complete disappearance of the Ph chromosome. The researchers have yet to find any toxic effects of the experimental drug. Their work is an important demonstration of how laboratory research can eventually be translated into the development of a powerful new therapeutic agent for cancer.

New Drug Extends Lives of Patients with Most Common Adult Leukemia
Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the United States, with

about 10,000 new cases occurring each year. The disease, which usually affects people over age 55, generally progresses slowly. In the early stages, patients commonly have no symptoms and may require no treatment for years. When the disease progresses, however, chemotherapy is warranted. There is no cure for CLL and patients with advanced disease live an average of not more than 2 years.

For decades, there have been no advances in the treatment of CLL. Yet, a recent clinical study coordinated by NCI has demonstrated that fludarabine, a chemotherapy developed in the 1980's, can extend the lives of patients with progressive CLL. The study compared the effectiveness of fludarabine with chlorambucil – the standard agent for CLL treatment – in 544 previously untreated patients. Fludarabine was significantly more active than chlorambucil, producing higher complete and overall response rates. Furthermore, responses to fludarabine were significantly more durable, lasting 29 months compared to 19 months for chlorambucil. There were no meaningful differences in toxicity between the two drugs. Because of these results, the approach to treating this disease is changing, and fludarabine is being used more often as a first-line treatment for patients with progressive CLL.

Early Hormonal Therapy Extends Lives of Prostate Cancer Patients

Prostate cancer is the most common form of cancer, other than skin cancer, among men in the United States and is second only to lung cancer as a cause of cancer-related death among men. Several treatment options are available including surgery, radiation, and drugs. The stage of disease and the patient's age and overall health are used to make treatment choices. Because male hormones (especially testosterone) can help prostate cancer to grow, drugs or surgery to reduce male hormone levels also can be used. This hormonal therapy is usually confined to patients with more advanced disease because of side effects. However, some researchers and clinicians have long questioned whether earlier use of hormonal therapy can prolong survival for patients who have not been cured by surgery or radiation.

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. A total of 98 patients were enrolled in the study between 1988 and 1993 and followed for an average of 7 years. At the end of the follow-up period, 7 of 47 men who received immediate hormonal therapy had died compared with 18 of 51 men in the observation group. Three of the deaths in the treatment group and 16 of the deaths in the observation group were due to prostate cancer. At the time of the last follow-up, 36 men in the treatment group (77 percent) and 9 men in the observation group (18 percent) were alive and had no evidence of recurrent disease.

The results of this trial, together with evidence from previous studies, support the hypothesis that early hormonal therapy may prolong the survival of men with prostate cancer. 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.

Experimental Technique Shows Promise in Treating Liver Metastases in Patients with Colorectal Cancer

Approximately 60 percent of patients with colorectal cancer experience metastasis of their cancer to the liver. Although surgery is commonly used to remove these liver metastases, there is currently no standard way to treat microscopic tumors (micrometastases) that remain after surgery or to prevent tumors from spreading to other organs. And, some patients have liver metastases that – because of their location, number, or other factors – cannot be surgically removed. Despite aggressive chemotherapy, life expectancy for patients with inoperable liver metastases of colorectal cancer ranges from 2 months to 2 years.

Results of two clinical trials support the use of hepatic arterial infusion (HAI) for more effective treatment of these liver tumors. HAI is an experimental technique for delivering high doses of chemotherapeutic drugs directly to liver tumors while minimizing toxicity to the liver and other organs. Unlike other organs, the liver has a dual blood supply; liver tumors get their blood supply largely from the hepatic artery, whereas normal liver cells obtain their supply from the portal vein. HAI works by infusing drugs through a catheter or pump in the hepatic artery. The technique recently has shown promising results in clinical trials conducted by two groups of NCI-supported investigators. One trial compared the efficacy of a combination of standard chemotherapy and HAI with standard chemotherapy alone in 156 patients who had undergone surgical removal of liver metastases of colorectal cancer. After 2 years, overall survival was 86 percent in the group treated with combined therapy compared with 72 percent in the group receiving standard chemotherapy alone. Survival free of recurrence of liver tumors was 90 percent and 60 percent, respectively. In the second trial, 34 patients with inoperable primary or metastatic liver tumors were treated with a variant of HAI known as isolated hepatic perfusion. Among patients with colorectal cancer, the response rate was 80 to 90 percent. The median duration of response was over 18 months. In most patients, treatment resulted in significant regression of bulky liver tumors. These studies demonstrate that patients with both operable and inoperable liver metastases of colorectal cancer can benefit from HAI.

Anti-Angiogenic Agents Show Promise in Treating AIDS-Related and Other Cancers

In one of the most compelling findings to date in a clinical trial of a treatment for an AIDS-related cancer, investigators recently reported that thalidomide is an effective treatment for AIDS-related Kaposi's sarcoma. Because this cancer is heavily dependent on the development of tiny new blood vessels for its growth (a process known as angiogenesis), scientists had hypothesized that therapies that block the formation of new blood vessels, such as thalidomide, could be particularly effective in combating this malignancy. Among the participating patients who received at least 5 weeks of therapy, nearly half (47 percent) saw their tumors shrink. In addition to suggesting an effective new treatment for Kaposi's sarcoma, this study is one of the first to establish that an anti-angiogenic drug can reduce an established tumor.

Progress with Antibodies as Anticancer Agents

Monoclonal antibodies are laboratory-produced proteins that can locate and bind to specific proteins expressed by cancer cells. NCI-supported researchers are exploring the use of a monoclonal antibody called C225 in cancer treatment. C225 binds to proteins that are frequently overproduced in cancer cells – epidermal growth factor receptors – and inhibits the growth of cancer cells. In a recent series of Phase I studies, C225 showed activity against epithelial tumors and head and neck cancer when given

alone or in combination with standard treatments. Treatment with C225 was well tolerated by patients. Investigators are currently studying the effectiveness of C225 in combination with other treatments against head, neck, and pancreatic cancers.

Genomics and Genetic Medicine

Anti-Apoptosis Gene is Overexpressed in Cancer Cells

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

NCI-supported investigators have discovered a gene that appears to be a critical regulator of apoptosis and to be particularly important in cancer. This gene, named *survivin,* is the smallest member of a family of genes known as apoptosis inhibitors. The investigators have demonstrated that *survivin* is abundantly expressed in many malignant tumors, including basal and squamous cell skin cancers, metastatic melanoma, and bladder cancer. However, it is not expressed in normal tissue adjacent to the tumors. The researchers have also shown in model tumor cell lines that blocking *survivin* expression results in spontaneous apoptosis. A recent genomic analysis found that *survivin* was invariably expressed in cancer but not in normal tissues. Other data suggest that *survivin* plays a key role in cell development by preventing apoptosis during cell division. When it is overexpressed, however, as it is in cancer cells, its anti-apoptosis function may allow cells that should have been destroyed to proliferate. Another line of investigation has shown that *survivin* is highly expressed in the newly formed blood vessels of tissue that forms over a healing wound. The growth of new blood vessels, or angiogenesis, is essential for tumor growth.

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

Gene Is a Critical Player in Tumor Metastasis

The most damaging change that can occur during cancer progression is the spread of cancerous cells to organs distant from the primary site of disease. In this process, known as metastasis, cells break off from tumors, enter the bloodstream, and travel to other organs, where they grow into new tumors. Metastasis is ultimately responsible for the deaths of most cancer patients, but it remains a poorly

understood process. Researchers do know that, in order to metastasize, tumor cells must complete a complex series of steps that involve numerous molecular changes. A complete understanding of the molecular basis by which tumors spread to distant organs is important to the development of new strategies to diagnose, control, and treat metastatic cancer.

NCI-funded investigators have now identified a gene that causes noninvasive, poorly metastatic melanoma cells to become invasive and metastatic. Using modern molecular technology that allows the analysis of several thousand genes at a time, the investigators examined genes expressed by mouse and human melanoma cells, some metastatic and some not, to identify genes involved in changing tumor cell behavior that might cause the cells to become highly invasive and metastatic. This gene analysis produced several promising candidate genes, one of which is *rhoC*, known to be involved in tumor cell motility and invasion. When *rhoC* was expressed in poorly metastatic human melanoma cells, the cells became highly motile and metastatic. In contrast, when *rhoC* expression in metastatic cells was inhibited, the cells became less motile and were poorly metastatic. The investigators are currently testing the hypothesis that *rhoC* can confer metastatic properties on other human tumor cells.

These results demonstrate that molecular characterization of tumor cells can provide more refined and clinically useful definitions of tumors by differentiating those that are malignant but noninvasive from those that are invasive and metastatic. Studies like these open opportunities to develop more effective strategies for diagnosis and treatment.

Predicting Lung Cancer by Detecting Methylated Genes

Lung cancer is the leading cause of cancer death in the United States and is expected to reach epidemic proportions throughout the world during this century. Although significant advances have been made in the identification of DNA markers for many types of cancer, a recent study by NCI-supported researchers may for the first time provide clues for developing such markers for early lung cancer. These molecular markers are unique signatures of cancer cells that can be used to detect cancer in its earliest stages, before it can be found by other means and when treatment is more likely to be successful.

An ideal DNA marker should be detectable early enough in the disease process for treatment to improve the patient's prognosis. It should also be easy to detect in a fluid or tissue that can be collected from patients without the need for invasive procedures. Because both current and former cigarette smokers have increased secretions, or sputum, from the bronchi, the branch-like passageways leading from the throat to the lungs, studies of DNA markers for lung cancer have focused on analyzing genes isolated from the sputum of former and current smokers with lung cancer.

Investigators focused on the *p16* and *MGMT* genes, both of which are good candidates for molecular markers of early lung cancer. The *p16* gene plays a key role in regulating cell cycles, and *MGMT* protects cells from the cancerous effects of substances like cigarette smoke. The researchers conducted the study using genetic material isolated from sputum samples of patients with a form of lung cancer known as squamous cell carcinoma (SCC). The patients included current and former smokers, as well as individuals exposed to radon through mining. The researchers found that when genes such as *p16* and *MGMT*, which normally help to protect against cancer, are in the presence of an extra

chemical group such as cigarette smoke, they become inactive, and cancer may be more likely to develop, a process called methylation. Methylation of one of these genes was found in the sputum of every one of the SCC patients studied and was seen not only at the time of diagnosis, but also in all the sputum samples that had been collected from 5 months to nearly 3 years *before* lung cancer could be clinically detected. Scientists' ability to detect methylation in genes therefore may hold great promise for finding lung cancer at a very early stage and may be useful for detecting other forms of cancer as well.

Bioengineering, Bioimaging, and Bioinformatics

During the course of their treatment and follow-up, cancer patients often undergo both computed tomography (CT) and positron emission tomography (PET) scanning. Each type of imaging provides physicians with distinct information on a patient's condition: a CT scan reveals the precise size, shape, and location of a tumor, while a PET scan's focus on metabolic function can indicate whether it is growing or shrinking.

Yet on its own, each form of imaging has its drawbacks. CT scanning cannot always capture the subtle details necessary to determine whether cancer may have spread. Similarly, PET scanning lacks the precision needed to pinpoint the location of a tumor. As a result, both types of scans may be required to obtain a complete picture of a patient's condition – and even then, physicians face the difficult task of matching up PET and CT scan results.

Recently, however, NCI-funded investigators put the final touches on an imaging system that aligns the CT anatomical scan and the PET functional scan and performs them both simultaneously, reducing the number of scans cancer patients must undergo and providing their physicians with a single set of test results.

After 8 years of testing and development and the creation of special computer software to control the two imaging processes simultaneously, the Food and Drug Administration in October 2000 approved the combined PET/CT scanner. When physicians begin using the new medical imaging system at cancer centers around the country in early 2001, it is expected to substantially improve their ability to diagnose cancer, determine how far it has spread, and track their patients' response to treatment.

Health Disparities: Biomedical and Behavioral Approaches

Study Supports Equal Treatment – Equal Outcomes Conclusions from Previous Studies
If discovered at an early stage, non-small-cell lung cancer is potentially curable by surgical resection. However, two disparities have been noted between black patients and white patients with this disease. Blacks are less likely to receive surgical treatment than whites, and they are likely to die sooner than whites. When NCI-supported researchers undertook a population-based study to estimate the disparity in the rates of surgical treatment and to evaluate the extent to which this disparity is associated with differences in overall survival for non-small-cell lung cancer patients, they were interested in two questions: Is there a difference in the rate of surgical treatment between white patients and black patients? and Does this discrepancy in part explain the difference in survival between black patients and

white patients with lung cancer?

Study patients were 65 years of age or older who were diagnosed between 1985 and 1993 with stage I or II non-small-cell lung cancer. The 10,984 patients in this study (860 black and 10,124 non-Hispanic white) were all Medicare recipients residing in 1 of the 10 study areas of the Surveillance, Epidemiology, and End Results (SEER) program. Data on the diagnosis, stage of disease, treatment, and demographic characteristics of the patients were obtained from the SEER database. Information on coexisting illnesses, type of Medicare coverage, and survival was obtained from linked Medicare inpatient discharge records. The rate of surgery was 12.7 percentage points lower for black patients than for white patients (64.0 percent vs. 76.7 percent), and the 5-year survival rate was also lower for blacks (26.4 percent vs. 34.1 percent). However, among the patients undergoing surgery, survival was similar for the two racial groups, as it was among those who did not undergo surgery. Furthermore, analyses in which adjustments were made for factors that are predictive of either candidacy for surgery or survival did not alter the influence of race on these outcomes.

These analyses suggest that the lower survival rate among black patients with early-stage, non-small-cell lung cancer, as compared with white patients, is largely explained by the lower rate of surgical treatment among blacks. Increasing the rate of surgical treatment for black patients would appear to be a promising way of improving survival in this group.

NEW ACTIVITIES

Advances such as those described above and the changes that underlie them are driving an evolution and rethinking of NCI's activities. These new initiatives are accelerating the pace of discovery, speeding our efforts to unravel cancer's intricacies, and addressing concerns of quality and disparities in cancer care, access to information, and research opportunity.

Tissue Array Research Program

Cancer researchers nationwide may soon be able to dramatically accelerate their work using a new tissue analysis technology. The new technology, developed by the National Human Genome Research Institute, makes it possible to store hundreds of very small tissue samples on a single laboratory slide, in a "tissue microarray." Unlike traditional tissue analysis tools, which allow scientists to examine only a few tissue samples at a time, or other types of microarrays that contain only DNA, tissue microarrays permit scientists to examine hundreds of tumor samples at once.

NCI's Tissue Array Research Program (TARP) began making tissue microarrays available to investigators across the country in the fall of 2000. Not only does this new technology have the potential to accelerate research by hastening the process of identifying the unique characteristics of cancer cells, but it also can provide investigators with greater flexibility in their studies. For example, tissue microarrays may include samples from many different types of tumors for screening purposes, or may contain tissues from various stages of a single kind of tumor for comparison studies.

Molecular Target Drug Discovery Program

Identifying, characterizing, and validating promising new molecular targets - i.e., potentially vulnerable sites in the cancer cell such as proteins, receptors, enzymes, or cellular pathways essential to cancer growth – is the first step in the process of developing targeted cancer drugs. This new approach to cancer prevention and treatment involves the development of agents that selectively take aim at newly identified molecules or pathways to block, delay, or arrest cancer progression.

To encourage creative investigation in this area, NCI will fund molecular target drug discovery grants to support (1) identification of novel molecular targets for prevention and treatment, (2) validation of targets as a basis for cancer drug discovery, and (3) development of tests to detect the effects of various agents on the targets. NCI also will support exploratory grants to help scientists gather preliminary data that will render these projects more competitive for the regular grant funding process; small business grants to help small businesses launch commercial products (e.g., tests to screen agents for their effectiveness against high-priority targets); and supplemental grants to enable NCI grantees to extend the goals of their active grants to include studies related to drug discovery.

Exploring Gene-Environment Interactions through Population Studies

Establishing significant and valid evidence for gene-environment interactions requires studies of large populations over long periods of time. NCI is pursuing two types of population studies for this purpose – cohort studies and case-control studies.

In cohort studies, researchers prospectively collect information on exposures to factors that might affect cancer risk. This type of study is useful for cancers that occur frequently enough to generate large sample sizes and is particularly useful – in fact sometimes the only means – for evaluating exposures and susceptibilities for which measurement may be altered by the presence of disease or its diagnosis or treatment. Participants are asked to provide biologic samples and then are systematically followed over time to determine who does or does not develop cancer. This information from large population groups provides strong indicators of the cancer risk associated with specified exposure and genetic profiles, opening doors for possible earlier detection for those at high-risk. Because such studies can be extremely costly and challenging to pursue, NCI is establishing a Cohort Consortium of investigators from around the world who already have high-quality epidemiologic data and stored sources of DNA on large numbers of individuals who are being followed for the development of malignancy. The Consortium will develop the resources and infrastructure needed to address gene-environment interactions in cancer etiology in a systematic and coordinated manner.

In case-control studies, researchers retrospectively examine exposure histories and genetic profiles of people who already have cancer and compare them with people who have not developed cancer. NCI is assembling a Case-Control Consortium to support large-scale studies of gene-environment interactions for less common cancers.

Quality of Cancer Care

In recognition of the importance of understanding and more effectively addressing concerns about the quality of care received by cancer patients at all stages of their experience, NCI has identified the Quality of Cancer Care as one of the NCI Challenge areas beginning in Fiscal Year 2002. Efforts at

NCI to evaluate the delivery of cancer care and track how variations in treatment affect patient outcomes include several new and ongoing initiatives. Of special significance is the upcoming identification of up to a dozen sites around the country that will form a consortium for tracking cancer care practice patterns and assessing outcomes in patients with lung and colorectal cancer. Researchers in this new Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium will identify newly diagnosed patients with lung and colorectal cancer, monitor the care they receive, and compare the results of their treatment. The data collected during the course of this project and subsequent analyses by consortium investigators are expected to permit a more in-depth assessment of cancer care and outcomes in a wider range of patient populations and delivery settings than any previous research effort. Findings from this project should also help explain why some groups of cancer patients may not be receiving optimal treatment and identify strategies for improving the quality of their care.

Other NCI initiatives aimed at improving the quality of care involve more studies of cancer care and outcomes among patients participating in the Medicare program. When linked with data on cancer incidence and survival from NCI's Surveillance, Epidemiology, and End Results Program, Medicare databases have proven to be such a very rich source of data on quality of care. For this reason, NCI plans to expand its research in this area, and extend it to the under 65 population, by creating similar databases of information from private insurers.

Health Disparities

In recognition of a growing society-wide concern over persistent health disparities between different population groups, and in conjunction with HHS and NIH-wide activities to address these disparities, NCI has also designated Reducing Cancer-Related Health Disparities as a special NCI Challenge in the Fiscal Year 2002 Plan and Budget proposal. A new Center to Reduce Cancer Health Disparities will oversee the implementation of the NCI's Strategic Plan to Reduce Health Disparities and efforts to find ways to translate research discoveries into the delivery of services that will reduce differences in health status and outcomes.

In April 2000, the Special Populations Networks for Cancer Awareness Research and Training project established a group of 17 universities, medical schools, and teaching hospitals to create and implement cancer control, prevention, research, and training programs in minority and underserved communities. The cooperative relationships established by the Networks with community groups over the next five years are expected to extend the reach of NCI's cancer awareness activities, encourage the participation of minority patients in clinical trials, and improve training and career development opportunities for minority investigators.

A similar initiative established formal partnerships between NCI-designated Cancer Centers and minority-serving institutions, such as historically black and tribal colleges, in the spring of 2001. The partnerships – which NCI is funding jointly with the NIH Office of Research on Minority Health – will help support and stabilize research projects and research training activities in minority-serving institutions, initiate long-term collaborations, and improve the effectiveness of Cancer Center research, education, and outreach activities.

OTHER AREAS OF INTEREST

Over the past few years, literally dozens of new opportunities for research have been created through the Phased Innovation Award, the Unconventional Innovation Program, and NCI's functional imaging initiatives. These programs enable researchers to develop, access, and use new technologies. In addition, initiatives like the Cancer Genetics Network, the Early Detection Research Network, the Mouse Models of Human Cancer Consortium, and the Specialized Programs of Research Excellence bring together researcher communities and their collective resources, allowing them to ask questions on a larger scale. By combining the efforts of engineering technology and biomedical science, we have been able to devise highly sophisticated imaging tools for detecting, diagnosing, and even aiding in the treatment of cancer patients. The development of common forms, terminology, and reporting requirements for use in cancer clinical trials is increasing our ability to do research on a large scale and with greater complexity. And, we now are able to store and disseminate data on thousands of tumor tissue samples, making cancer information instantly available to researchers around the world.

As we look ahead to Fiscal Year 2002, we anticipate significant ongoing and new activity concentrated in our Centers, Networks, and Consortia, as well in areas of special concern such as genetics, technology development, surveillance research, drug discovery, clinical trials, and bioinformatics.

Centers of Research Excellence

Centers of Research Excellence bring together interdisciplinary and translational research teams to focus on specific diseases, treatment approaches, biological processes, and basic and behavioral scientific research areas. Their purpose is to address emerging scientific opportunities and move them forward at an accelerated pace. The first group of these centers, the Specialized Programs of Research Excellence (SPOREs), were created in 1992 and focused on specific cancers. They continue to serve as hubs for translational research by providing an environment for dynamic interaction among laboratory, clinical, and population researchers to most efficiently move research toward application. SPORE centers have been established in breast, prostate, lung, gastrointestinal, and ovarian cancer. NCI plans to expand this program to include additional centers in breast and prostate cancer and to add new ones in head and neck cancer, brain cancer, and lymphoma.

The success of the SPORE has spurred NCI to establish similar programs using this blueprint. These include Transdisciplinary Tobacco Use Research Centers, *In Vivo* Cellular and Molecular Imaging Centers, and Interdisciplinary Research Teams in Molecular Target Assessment. Plans are underway to create Centers of Excellence in Cancer Communications Research (CECCRs) and Centers for Population Health, both areas where the results of the research can be used to narrow the gap between discovery and application and to reduce health disparities among our citizens. The interdisciplinary research conducted through the CECCRs will address the many complexities of cancer communications – from how to increase people's understanding of information about cancer to the implications of the rapid evolution of new media to understanding and addressing the needs of diverse audiences. The Centers for Population Health will expand understanding of the social and environmental causes of cancer-related health disparities and the psychosocial, behavioral, and biological factors that mediate them and develop hypotheses for cancer control research at the individual, social, institutional, and policy levels.

Early Detection Research Network

Designed as a national consortium to support collaborative research among academic and industry investigators with varied expertise, the Early Detection Research Network (EDRN) is an innovative, investigator-initiated project that aims to identify and evaluate molecular markers and technologies for earlier detection and risk assessment for all major cancers. The EDRN is striving to link the discovery of biomarkers directly to the next steps in the process of developing early detection tests. These discoveries will lead to work that confirms and improves the accuracy of the markers and then to early clinical validation of the tests. The program is unprecedented in its charge and scope – to develop approaches for identifying people at high-risk for cancer that will ultimately allow medical practitioners to focus on prevention rather than on treatment. EDRN research is funded through:

- Eighteen Biomarker Developmental Laboratories to identify, characterize, and refine techniques for finding molecular, genetic, and biologic early warning signals of cancer.
- Three Biomarker Validation Laboratories that serve as intermediaries between the Biomarker Developmental Laboratories and general clinical settings. The role of the validation laboratories will be to standardize tests and assure reproducibility, and then scale up production and ready the best biomarker tests for clinical trials.
- Nine Clinical/Epidemiology Centers that focus on providing the network with blood, tissue, other biological samples, and medical information on families with histories of cancer. These libraries will serve as vital resources for the large-scale evaluation of cancer biomarkers.
- A Data Management and Coordination Center to develop standards for data reporting and research new statistical methods for analyzing biomarkers.

Mouse Models of Human Cancer Consortium

Mouse models of human cancers are invaluable, multifaceted tools that enable scientists to investigate the development and behavior of cancer; test new approaches to detection, diagnosis, and imaging; and evaluate prevention and treatment. To ensure that state-of-the-art techniques and standards are developed to derive and validate mouse models (mice with cancers that mimic the major human cancers that can be inherited), NCI has created the Mouse Models of Human Cancer Consortium (MMHCC). Composed of 20 multidisciplinary groups of investigators from institutions across the country, the

MMHCC capitalizes on the expertise and judgement of its members to devise and apply innovative technologies to develop, refine, characterize, and validate mouse models. The consortium approach enables each participating team to pursue its most innovative ideas and experimental approaches while interacting with other member teams to foster the rapid exchange of ideas, information, and technology. MMHCC participants currently are working to develop and evaluate mouse models for breast, prostate, lung, ovary, skin, blood and lymph system, colon, and brain cancers. These models will be made available to investigators across the cancer research community.

The MMHCC forum program is the primary form of outreach for the Consortium. It is used to sustain discovery in all aspects of cancer research by engaging broad community perspectives about the design and application of mouse models through think tanks, discussion groups, task forces, and focus groups. For example:

- The Leukemia and Lymphoma Models Focus Group has been working on standards, common vocabulary, and validation parameters.
- The Ovarian Models Think Tank developed a priority list for collaborations to derive models where none presently exist and to apply evaluation standards to available models.
- The MMHCC/Pharma/Biotech Intellectual Property Roundtable is exploring solutions to impediments to productive interactions between the private sector and academic researchers.
- The Neuro-Oncology Models Forum shares information on the pathology and biology of nervous system tumors and debates priorities for future models. The Forum developed a response to the NCI Brain Cancer Progress Review Group recommendations on pre-clinical models.
- The Mouse Models for Prevention Focus Group combines leadership from NCI Intramural researchers and MMHCC investigators to derive mouse models that can inform the search for molecular targets for prevention and support testing of the resulting strategies.

Additional forum meetings planned for the near future include a Cutaneous Malignancies Think Tank; a Small Animal Imaging Forum; a Complex Traits and Genetic Modifiers Forum; a Mouse Models of Pancreatic Ductal Cancer Task Force; a Prostate Cancer Models Focus Group; and a Predictive Pre-Clinical Models Discussion Group.

The Cancer Genome Anatomy Project

As normal cells are transformed into cancer cells, their "signatures" change. Understanding what these changes are and with what genes they are associated will someday enable us to recognize the major steps of tumor development. To address this need, the NCI Cancer Genome Anatomy Project (CGAP) is combining the newest cost-effective high-throughput technologies to identify all the genes responsible for the establishment and growth of cancer. Initially, we focused on cells that directly give rise to tumors and placed emphasis on five major types of cancer. Now with the necessary infrastructure established, we are positioned to examine a wider variety of cancers and to extend our investigations to include cells that play key supporting roles in cancer development. These include cells that form the tiny blood vessels that feed tumors, cells that metastasize and the tissues that support those metastases, as well as body fluids that might contain early indications of cancer development. Nearly 41,000 new genes have been discovered through CGAP's main component, the human Tumor Gene Index.

Many types of cancer are complex genetic diseases. That is, they result not from changes in a single gene but from the combined, small effects of many genes and the interaction of these genes with environmental, hormonal, and other factors. An important step toward identifying all of the major genes involved in cancer is detecting the polymorphisms, the variations in a gene sequence that give rise to protein variants or influence the expression of the gene. NCI recently launched the Genetic Annotation Initiative (GAI), a component of CGAP, to systematically explore and apply technology for the identification and characterization of polymorphisms important in cancer. The identification of gene variations coupled with the development of laboratory assays to characterize these variations will extend the use of genetic information for improving our understanding of common cancer and its related phenotypes.

Stimulating Technology Development and Application

NCI has taken advantage of recent advances to create several programs to support near- and long-term technology development in areas that promise to speed and enable cancer research. These efforts will be used to move ideas down the pipeline and to seed novel, high-impact technologies. The potential for some new technologies may take many years to be realized, but work on them must continue now.

To develop and apply technology to advance molecular signatures research, NCI recently created the Innovative Molecular Analysis Technologies (IMAT) program. This program supports research to develop and carry out pilot applications of instruments, techniques, and analysis tools that can be used to conduct molecular analyses of tumor samples. For example, the cost-effective, automated tools developed through this program will enable scientists to identify DNA alterations in tumor samples, monitor the expression of genes and their cellular products, determine the function of various cellular proteins, and identify and monitor cellular pathways involved in cancer. These methods also are being used in high-resolution cellular or molecular imaging research, analysis of tissue samples, development of preclinical models, clinical investigations, and population-based studies for improving our ability to effectively analyze large volumes of samples and data. More than 80 grants have been awarded through this program.

The IMAT program uses the innovative Phased Innovation Award and Phased Technology Application Award mechanisms. The first allows expedited review of technology research from the evolution of innovative concepts through feasibility testing and ultimately to full-scale development. The second fosters the translation of emerging technologies from evaluation to pilot application, speeding the adoption of near-term technological opportunities, once researchers have reached certain negotiated milestones in their projects.

To spur development of daring technologic improvements in cancer treatment and detection in the 21st century, NCI also created the Unconventional Innovations Program (UIP). The program focuses on stimulating the development of radically new technologies in cancer care that can transform what is now impossible into the realm of the possible for detecting, diagnosing, and intervening in cancer at its earliest stages of development. Started in 1999, UIP is targeted to invest $48 million over the next 5 years. UIP does not target incremental improvements to the state of the art in technology but actively recruits

the interest and involvement of investigators from disciplines that have not traditionally received NCI support and encourages these scientists to develop new technologies or make quantum improvements to existing technologies. Five UIP contracts for "Novel Technologies for Noninvasive Detection, Diagnosis, and Treatment of Cancer" have been awarded to date.

Cancer Surveillance Research

Identifying and tracking rates and trends in cancer and monitoring the factors that influence these changes are crucial to our understanding of how to prevent and control cancer. Our primary means for tracking these trends is the NCI Surveillance, Epidemiology, and End Results (SEER) database. For over 25 years, SEER has enabled us to identify geographic areas with higher than average rates of cancer, to study patterns and outcomes of cancer care, and to identify risk groups for research and public health intervention. In FY 2001 NCI substantially expanded the SEER Program to add three states **B** Louisiana, Kentucky and New Jersey **B** and the remaining portions of California not already under SEER coverage. The contracts were awarded through competitive selection and peer review, with emphasis on (1) coverage of populations for which limited data currently exist and (2) data quality that meets SEER standards and reporting requirements. Overall, SEER coverage will increase from 14 percent to 26 percent of the U.S. population, or from about 35 million to over 65 million people. For minorities, the SEER expansion increases coverage to 24 percent of African Americans, 44 percent of Hispanics, 42 percent of American Indians and Alaska Natives, and 59 percent of Asian and Pacific Islanders. Also, during the next three years, NCI staff will work closely with the CDC staff who manage the National Program of Cancer Registries (NPCR) to coordinate parallel implementation of the SEER geographic expansion to increase the number of population-based registries with SEER quality data.

To further explore the causes of cancer, NCI supports epidemiologic studies utilizing the *NCI Atlas of Cancer Mortality in United States, 1950 -1994* and other population-based data systems on cancer incidence. The study of geographic variation of cancer rates as identified through data systems such as the Cancer Atlas assist researchers in developing hypotheses about the role of lifestyle and other environmental factors that affect cancer risk. NCI also plans to support research initiatives that use geospatial, mapping, and other analytical methods applied to existing population-based data systems of environmental and sociocultural risk factors to develop hypotheses for more in-depth studies of cancer causation.

In addition, NCI is working with public and private partners to build a comprehensive and integrated surveillance system to monitor tobacco control progress at the local, regional, and national levels. Through the To*bacco Use Supplements to the Current Population Surveys*, the Census Bureau made final data from the 1990s available in the Winter of 2001 as a public use data resource. NCI will provide supplements to existing tobacco control grants to encourage researches to analyze these data.

Drug Discovery Activities

Because academic institutions commonly lack the capacity to develop drugs, promising ideas and novel treatment interventions often cannot move forward in the drug discovery process. The *Rapid Access to Intervention Development* (*RAID*) program is designed to place NCI's drug development resources at

the service of investigators with molecules that hold promise for cancer treatment and facilitate movement of new discovery into the clinic. By providing the resources needed for preclinical development of drugs and biological agents, this program removes the most common barriers between laboratory discovery and clinical testing. Unlike other NCI drug-discovery programs, products developed through the RAID program are returned directly to the originating laboratory for clinical trial testing. Fourteen projects have been funded over the past two years through this program.

While RAID focuses on cancer treatment, the *Rapid Access to Preventive Intervention Development (RAPID)* program provides funding and resources to scientists working to develop agents to prevent, reverse, or delay cancer development. Like RAID, RAPID is designed to quickly move novel preventive molecules and concepts from the laboratory to the clinic for efficacy testing in clinical trials. RAPID will accelerate the development process for preventive agents by providing investigators with the contract resources needed for preclinical and early clinical drug development, ensuring the efficient translation of promising discoveries even when investigators and their institutions lack the requisite development capacity or clinical expertise. To date, seven projects have been funded through this program.

There are many steps involved in turning a potential anti-cancer agent into a "drug" appropriate for human use. Following initial discovery, efficiency testing and optimization, lead agents must undergo a series of rigorous evaluations that culminate with a clinical trial. As a result, drug discovery can take years and an investment of several million dollars. To encourage and support the participation of small businesses in this process, NCI has established the *Flexible System to Advance Innovative Research (FLAIR)*. FLAIR will expedite cancer therapeutic development by small businesses by providing the budgets and time required to support research at all stages of drug and vaccine development.

Clinical Trials

To ensure that a national cancer clinical trials program is poised to address the most important medical and scientific questions in prevention and treatment quickly and effectively requires state-of-the-art approaches and support systems. These must be coupled with an outreach program that ensures communication, education, and access for all populations who can benefit from clinical trials. To ensure that all these requirements are met, NCI has been restructuring and reorganizing its system of cancer clinical trials. These efforts are designed to ensure that the most promising laboratory results are quickly identified and tested and that proposals for major clinical trials involving 1,000 patients or more (Phase III trials) are not only reviewed but prioritized.

Considerable effort has also been made to increase the accessibility of clinical trials. These include establishing payer and provider partnerships and agreements with federal government departments and health plan providers for covering the costs of clinical trials; promoting coverage for Medicare recipients; and developing educational materials for physicians and patients.

In addition, NCI continues to expand the role of its new Cancer Trials Support Unit in reducing the administrative requirements for conducting clinical research and increasing access to clinical trials for patients and physicians. Initiated in 1999 as a pilot project, the Cancer Trials Support Unit will

introduce a remote-entry data collection system in 2001 to help streamline information collection and reporting. In another pilot project, NCI introduced a central Institutional Review Board (IRB) in the spring of 2000 to review the patient protections planned for selected multi-center clinical trials. If its efforts to reduce the administrative burden on participating institutions and ensure that patients are fully informed of the risks and benefits of participating in clinical trials prove successful, the role of the central IRB is expected to gradually expand until it encompasses all multi-center cancer clinical trials.

Bioinformatics

To support the information collection and sharing needs of an array of research programs both current and planned, NCI continues to build its cancer information infrastructure. Using the rich and diverse collection of data generated through the various components of the Cancer Genome Anatomy Project, NCI has created an integrated model of cancer-related genomic data and developed a Web portal that permits researchers to explore CGAP data for information such as gene expression patterns in different tissue types or gene variants in the population. NCI has also developed and implemented a modular computer program that assists in the rapid development, deployment, integration, and maintenance of NCI initiative-specific Web sites. This program has been used to deploy the prototype Web sites for the CGAP portal, the Mouse Models of Human Cancer Consortium, and the Director's Challenge. In support of the CGAP Web portal, NCI also has developed a prototype for an open source-based informatics architecture that facilitates the retrieval and integration of data distributed among multiple, independent data sources. Users are provided with the program code, allowing them to modify it at a fundamental level. This kind of effort must be ongoing for our research efforts to keep pace with the changing world of informatics.

AIDS Research

More than 30 percent of all AIDS patients develop some form of cancer during the course of their illness, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical or anal cancer. In its commitment to combating AIDS-related cancers, the National Cancer Institute ranks second among the NIH Institutes in its funding of AIDS research, following only the National Institute of Allergy and Infectious Diseases. The NCI's programs of intramural and extramural research encompass basic research on HIV and other retroviruses associated with cancer, developing and testing vaccines, and specific AIDS-related cancers and their treatment. In addition to its direct support of research, the NCI also provides funding for vital research resources, such as the development of animal models of AIDS and the collection of tissue samples from AIDS-related cancers. To coordinate clinical testing, the NCI also supports the AIDS Malignancy Consortium, a group of investigators conducting clinical trials on AIDS-related cancers at 15 sites around the country.

INNOVATIONS IN MANAGEMENT AND ADMINISTRATION

Cancer research and administration have continued to benefit from the adoption of Internet technologies. However, this year's featured innovations also reflect modern management demands which seek to streamline or eliminate paperwork, ensure accountability through results-based management, and address crucial recruitment and retention efforts.

External Review of NCI Business and Administrative Units

NCI is developing a process for conducting external reviews for each of its business and administrative units on a 4-year cycle. We seek to ensure accountability for our major management goals: (A) to facilitate the elimination of cancer – giving our customers what they need, when they need it; and (B) to be prudent and effective stewards of public funds. The review will examine how each unit focuses on results, fosters innovation, partners with scientists, balances the need for results with the demands of stewardship, and manages resources effectively. A former New Zealand Cabinet Minister, a pioneer in the application of results-based management to government, serves as an advisor to the current administration on this subject.

Expedited Board Concurrence and Early Grant Award Activity

In response to NIH's FY2000 GPRA initiatives and in conjunction with the results-based management movement, top-rated grant applications are posted to a secure web site for early review by members of the National Cancer Advisory Board. Immediately upon a grant's on-line approval by the Board and the relevant Program Director, the Grants Administration Branch sends an "Intent to Pay" letter to the grant applicants, significantly expediting their notification. Some of these grants are then awarded with start dates earlier than originally requested, accelerating the progress of the best cancer research efforts.

Institutional Grant Funding Agreement

NCI staff spearheaded the proposed NIH Institutional Funding Agreement initiative through which NIH and participating grantees will enter into renewable agreements. When fully implemented, grantees and NIH staff will process "R01 (snap) type 5" grants electronically. This will significantly reduce processing time and the cost associated with the grant application process to both the government and grantees.

Information Technology: Network Services and Training Program

We continue to enhance IT services to both scientific and management staff. Through Scientific Storage programs we are addressing the considerable data storage needs of our researchers; work in the areas of genetics and imaging demand significant information resources. We currently store over 1.5 terabytes of scientific data. Accompanying this increase in data storage is the implementation of security and performance enhancements for web sites and network operations. Finally, all staff have access to various computer training opportunities for skills and career enhancement. An objective is to reduce the number of calls to the NCI help desk through a better-trained workforce, resulting in reduced overall cost to the NCI.

Orientation Program

To better integrate our core values, we are changing how NCI welcomes new staff through the creation of a one-day, centralized orientation program. This program will guide new staff through the organization and familiarize them with important tools. Special emphasis will be placed on computer training, ethics training, and introduction to key NIH resources.

Recruitment and Retention Study

NCI's analysis of its ability to recruit and retain top-caliber scientists provided the basis for an Institute-wide pay study. The ongoing pay study will include a market-based pay comparison analysis of all NCI

positions to assist us in designing a compensation program that will compete effectively with the private sector. The study will also ensure pay equity through the development of clear guidelines and criteria that reflect industry/academia pay standards. Additionally, the recruitment/retention analysis resulted in the elimination of some central NIH hiring reviews and the transfer of increased appointment and compensation authorities from NIH to the Institutes. The goal is to create a streamlined procedure that reduces overhead costs and expedites the appointment process.

Academy for Career Excellence

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

NIH IntraMall

One of the government's first e-commerce efforts, the IntraMall was created and is run by the NCI. This program and its attendant cost-savings and efficiencies continues to grow. During Fiscal Year 2000, this initiative was recognized with the National Performance Review's "Hammer Award," the Center of Excellence for Information Technology's "Award for Best Practices in Applications of Information Technology," the Government IT Leadership Award, and the Association of Government Accountants' "Best Practices" award for the implementation of an emerging novel technology in federal, state, or local governments.

STORY OF DISCOVERY
Targeting Breast Cancer with Herceptin

In the ongoing fight against breast cancer, September 25, 1998 stands as an important milestone. On this date, the U.S. Food and Drug Administration (FDA) approved a new drug called Herceptin, as a treatment for late stage breast tumors. The approval of a new cancer drug always inspires new hope for cancer patients, but Herceptin – one of the first drugs to successfully attack cancer at its genetic roots – generated an exceptional wave of excitement throughout the cancer community. Its approval heralded the arrival of a revolutionary new class of drugs that thwart cancer by taking aim at the molecular changes that cause a cell to change from normal to cancerous. For many women, Herceptin has become a powerful weapon in their struggle against breast cancer.

Laying the Foundation

Herceptin's development is grounded in the molecular biology revolution that began about thirty years ago. Drs. J. Michael Bishop and Harold Varmus, investigators at the University of California /San Francisco back in 1976, were pioneers in showing that cancer is a genetic disease that develops when normal genes that control critical functions in a cell become altered. These "oncogenes," cause cells to lose some of their normal controls on growth, to multiply recklessly, and develop into a potentially life-threatening tumor. The Bishop and Varmus Nobel Prize-winning discovery offered scientists an unprecedented glimpse at the true nature of a cancer cell and changed the course of cancer research. It established a promising, new research path aimed at developing an accurate and detailed picture of the molecular changes that occur during a tumor's development and devising new ways to block or reverse these changes to prevent and treat cancer.

The discovery of oncogenes also launched an ardent search among cancer researchers to identify and isolate specific cancer-associated genes and to determine how their actions cause a normal cell to become cancerous. One of these investigators was Dr. Dennis Slamon, of the University of California/ Los Angeles. Slamon's studies, like those of many cancer researchers in the early 1980s, focused on screening tissue for cancer-associated genes. Researchers surmised that identifying the corrupt cancer genes and their corresponding proteins would provide critical insights into what was going wrong within the cancer cell. Unlike his colleagues, however, Slamon believed that human tissue – not animal tissue or cell lines – was the best place to screen for these genes. To enable his studies, he generated a human tissue bank of cancerous tissue discarded from diagnostic biopsies, in the hope that he might use this tissue someday to screen for altered genes.

Discovery of a Genetic Flaw

The process of screening for genes is usually a tedious and time-consuming fishing expedition, particularly in human tissue. In 1986, however, Slamon's efforts were advanced by several strokes of good fortune. Through collaboration with the biotechnology company Genentech, Inc., Slamon received several cloned genes that carried the genetic coding for growth factors – chemicals in the body that signal cells to grow and divide. When he tested the cloned genes against tissue samples from his tissue bank, he had a great success: One of the clones, known as the Human Epidermal Growth Receptor No. 2 gene or *Her-2/neu*, matched genes in certain breast and ovarian tumor samples.

Slamon next needed to confirm that the gene actually plays a role in cancer development. To answer this question, he and his colleagues studied DNA from breast cancer tissue to determine whether the *Her-2/neu* gene is altered, and if so, what effect it has on the cell. They discovered that the gene was changed, causing the affected cells to dramatically "overexpress," or overproduce normal Her-2/neu receptors. Affected cells become overloaded with signals to grow and divide – to become cancerous. A further review of clinical data revealed that elevated levels of the Her-2/neu receptor protein occurs in 25 to 30 percent of breast cancer cases, and in these cases, the cancer is particularly aggressive. Women with these tumors have shorter disease-free survival times, relapse more quickly, develop metastases more quickly, are less responsive to traditional treatments, and die more quickly once their cancer is diagnosed.

The Search for a Targeted Treatment

Sensing the magnitude of the *Her-2/neu* discovery, Slamon next focused all of his professional efforts on studying the gene and finding a treatment that targeted its activities. The *Her-2/neu* gene encodes a growth factor receptor that helps relay a signal that tells a cell to divide, and because of the receptor's accessible position on the cell surface, it is a prime target for a therapeutic. He and his colleagues theorized that developing an effective monoclonal antibody would be the quickest route to finding a useful therapeutic. Monoclonal antibodies, which are engineered in a

laboratory, possess similar characteristics to naturally occurring antibodies: Both selectively attack a target cell (for example, a virus, bacteria, or cancer cell) by binding to a specific protein, or antigen, on the cell's surface, leaving healthy cells unscathed. Monoclonal antibody technology offers the opportunity, however, to continuously produce thousands of uniform copies of an antibody targeted to a selected protein. The researchers began to test a series of monoclonal antibodies engineered to attach to the Her-2/neu protein on the surface of breast cancer cells. Their efforts paid off when a monoclonal antibody developed by Genentech effectively shut down the Her-2/neu receptor's actions and stopped the growth of cancerous cells in cell culture, without harming normal cells.

This laboratory success confirmed the link between the mutant *Her-2/neu* gene and an aggressive form of breast cancer and laid the foundation for a revolutionary new therapy for breast cancer. Yet, the scientists knew that monoclonal antibodies had serious drawbacks that had caused them to fail many times before as potential cancer treatments. At this time, monoclonal antibodies were difficult and expensive to produce in the large quantities needed. And, because they were generated in mice, the human immune system often marked them as foreign invaders and destroyed the antibodies before they could reach the cancerous target. But good fortune was once again with Slamon and his team. Shortly after the researchers found their effective monoclonal antibody, several biotechnology companies unveiled a new technology that could "humanize" mouse monoclonal antibodies. Using this new approach, the scientists successfully "humanized" the monoclonal antibody to the Her-2/neu receptor. This considerable accomplishment readied the monoclonal antibody for clinical tests to determine its safety and effectiveness in humans.

Clinical Trial Testing

Clinical trials for Herceptin began in 1990. Phase I trials showed that the new drug could effectively reach tumors and was relatively nontoxic. The first Phase II trials produced some positive results for more than half the trial participants and unexpectedly produced complete cancer remission for one woman. A second Phase II trial tested the Herceptin coupled with the chemotherapy agent, cisplatin, produced similar results. The Phase III trial included more than 600 women with metastatic breast cancer and excessive Her-2/neu production. For these women, treatment with Herceptin alone produced encouraging results even for the very aggressive metastatic breast cancer. Of 222 participants, four percent experienced complete disease remission, 26 percent had partial remission, and 16 percent experienced slowed disease progression and tumor shrinkage. For more than 25 percent of 469 women treated with Herceptin in combination with chemotherapy, cancer progression had stopped at one year compared to 10 percent of the women treated with chemotherapy alone. Adding Herceptin to chemotherapy also dramatically increased the number of women who had a partial response or tumor shrinkage compared to chemotherapy treatment alone. Moreover, Herceptin produced its positive effects without causing several of the common debilitating side effects of hair loss, fatigue, and mouth sores. The results of the clinical trials demonstrated that, although Herceptin is not likely to cure women with metastatic breast cancer, it can prolong patients' lives and improve their quality of life. The FDA agreed to give fast-track consideration to Herceptin and in September 1998, approved the drug as a treatment for metastatic breast cancer.

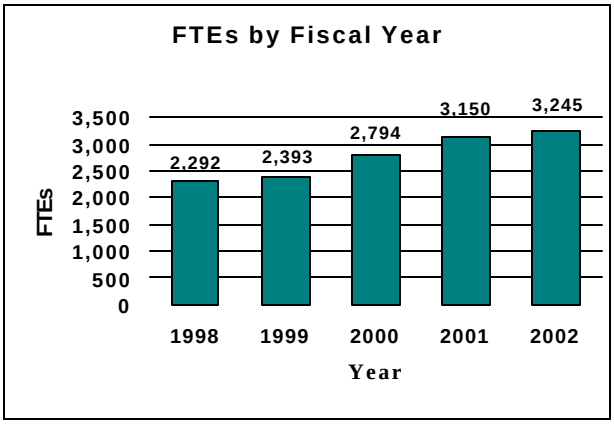
A New Drug Comes of Age

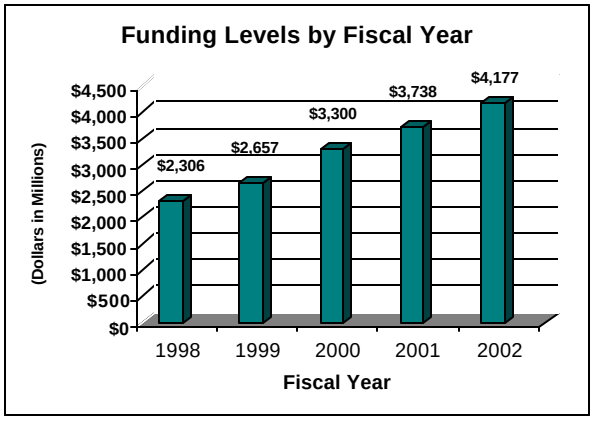
The 1998 approval, which came only 12 years after Slamon and his colleagues began to study the *Her-2/neu* gene, is a testament to good science, serendipity, the dedication of talented researchers and physicians, and the exceptional courage of scores of women who participated in clinical trials. The drug's favorable effect on breast cancer now has stimulated a number of clinical trials sponsored by the National Cancer Institute (NCI) that are evaluating whether Herceptin combined with other chemotherapies may improve treatment outcomes for other Her-2/neu expressing cancers. These include gastric, endometrial, salivary gland, prostate, colorectal, ovarian, non-small cell lung, and pancreatic cancers. NCI also is sponsoring two major studies to test the possibility of adding this agent to standard chemotherapy in earlier stages of breast cancer to enhance survival. NCI also is supporting studies of other Her-2/neu antibodies and other monoclonal antibodies targeted against specific proteins found on cancer cells.

Herceptin's significance extends far beyond its actions as a breast cancer drug. It represents a new era in cancer prevention and treatment. With the evolution of molecular biology and the emergence of new technologies, we are gathering remarkable knowledge about the molecular changes that occur during a tumor's development. We now can exploit this knowledge to develop less toxic and more effective approaches that target these changes to slow, stop, and prevent all types of cancer.

BUDGET POLICY

The Fiscal Year 2002 budget request for NCI is $4,177,203,000, including funds for AIDS research, an increase of $439,275,000 and 11.8 percent over the FY 2001 level, and $877,585,000 and 26.6 percent over FY 2000. A five year history of FTEs and Funding Levels for NCI are shown in the graphs below:





One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2002 request provides average cost increase for competing RPGs equal to the Biomedical Research and Development Price Index (BRPDI), estimated at 4.3 percent. Noncompeting RPGs will receive increases of 3 percent on average for recurring costs. In FY 2002, total RPGs funded will be 4,953 awards, an increase of 516 awards over the FY 2001 estimate, the highest annual total ever awarded by NCI.

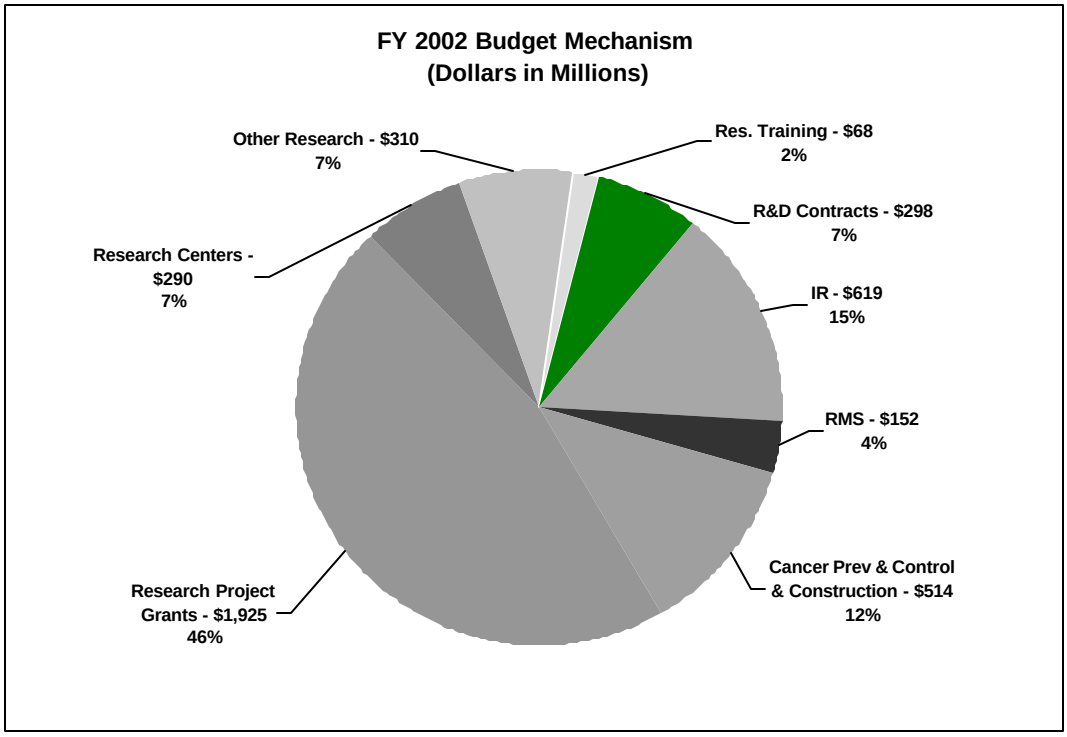
Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2002 request, NCI will support 1,600 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over Fiscal Year 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

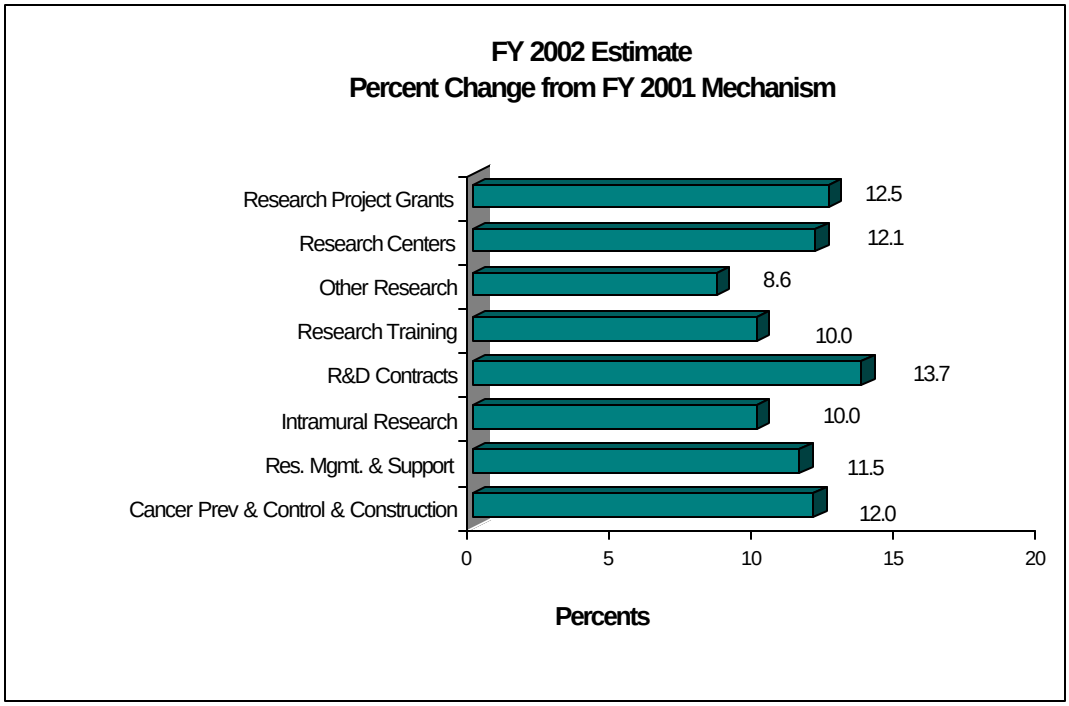
NCI's many research activities and initiatives require a supporting management and administrative infrastructure which, in large part, is funded through the Research Management and Support (RMS) mechanism. Since FY 1995, RMS funding has decreased from 5 percent of the budget to 3.6 percent in 2000. To provide the best balance of needs and resources, NCI's FY 2002 request maintains the RMS funding level at 3.6 percent of the total request, an increase of 11.5 percent. This funding level supports initiatives that include:

- Restructuring and increasing the capacity of our clinical trials program.
- Expanding our ability to support research in cancer imaging techniques that improve early detection, diagnosis, treatment, and prevention of cancer.
- Expanding NCI's informatics infrastructure to enhance information and resource exchange among researchers, clinicians, and the public.

- Improving our ability to define, monitor and ultimately help reduce cancer health disparities.

The Fiscal Year 2002 request includes funding for 99 research centers and SPORES, 762 other research grants, and 159 R&D contracts. The R&D contracts mechanism also includes support for the Extramural Clinical and Pediatric Loan Repayment Programs. The mechanism distribution by dollars and by percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

MECHANISM	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,101	$1,050,107,000	3,176	$1,167,861,000	3,414	$1,370,046,000
Administrative supplements	(266)	23,721,000	(327)	25,066,000	(330)	26,415,000
Competing:						
Renewal	354	158,799,000	405	179,809,000	385	180,549,000
New	763	233,128,000	832	261,013,000	810	263,390,000
Supplements	2	231,000	4	1,142,000	0	0
Subtotal, competing	1,119	392,158,000	1,241	441,964,000	1,195	443,939,000
Subtotal, RPGs	4,220	1,465,986,000	4,417	1,634,891,000	4,609	1,840,400,000
SBIR/STTR	306	67,090,000	330	76,000,000	354	85,120,000
Subtotal, RPGs	4,526	1,533,076,000	4,747	1,710,891,000	4,963	1,925,520,000
Research Centers:						
Specialized/comprehensive	82	221,351,000	92	258,658,000	99	289,878,000
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	82	221,351,000	92	258,658,000	99	289,878,000
Other Research:						
Research careers	317	42,469,000	358	52,088,000	380	57,828,000
Cancer education	83	16,821,000	82	19,819,000	86	21,671,000
Cooperative clinical research	140	144,608,000	145	159,964,000	150	173,386,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	3,341,000	0	4,178,000	0	4,638,000
Other	113	27,036,000	143	49,484,000	146	52,562,000
Subtotal, Other Research	653	234,275,000	728	285,533,000	762	310,085,000
Total Research Grants	5,261	1,988,702,000	5,567	2,255,082,000	5,824	2,525,483,000
Training:	FTTPs		FTTPs		FTTPs	
Individual awards	165	5,720,000	165	6,326,000	165	6,959,000
Institutional awards	1,435	50,459,000	1,435	55,774,000	1,435	61,351,000
Total, Training	1,600	56,179,000	1,600	62,100,000	1,600	68,310,000
Research & development contracts	138	236,308,000	151	261,950,000	159	297,825,000
(SBIR/STTR)	(4)	(406,000)	(4)	(450,000)	(7)	(3,251,000)
	FTEs		FTEs		FTEs	
Intramural research	1,790	509,023,000	1,908	563,130,000	1,965	619,443,000
Research management and support	793	116,912,000	783	136,398,000	807	152,084,000
Cancer prevention & control	211	388,994,000	459	456,268,000	473	511,058,000
Construction		3,500,000		3,000,000		3,000,000
Total, NCI	2,794	3,299,618,000	3,150	3,737,928,000	3,245	4,177,203,000
(Clinical Trials)		(613,954,000)		(673,500,000)		(740,000,000)

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:								
Cancer causation	777	$871,079	734	$888,662	771	$1,012,734	37	$124,072
Detection and diagnosis research	204	228,818	233	283,147	240	316,244	7	33,097
Treatment research	818	916,147	871	1,056,913	878	1,155,373	7	98,460
Cancer biology	475	532,206	522	631,780	542	712,256	20	80,476
Subtotal, research	2,274	2,548,250	2,360	2,860,502	2,431	3,196,607	71	336,105
Resource development:								
Cancer centers support	199	223,430	215	261,125	222	292,624	7	31,499
Research manpower development	107	120,140	114	139,019	117	153,427	3	14,408
Construction	3	3,528	2	3,011	2	3,022	0	11
Subtotal, resource development	309	347,098	331	403,155	341	449,073	10	45,918
Cancer prevention and control	211	404,270	459	474,271	473	531,523	14	57,252
Total	2,794	3,299,618	3,150	3,737,928	3,245	4,177,203	95	439,275

Note: Includes FTEs associated with HIV/AIDS research activities.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

2001 Estimated budget authority				$3,737,928,000
2002 Estimated budget authority				4,177,203,000
Net change				439,275,000
	2001 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$203,648,000		$3,727,000
b. Annualization of January 2001 pay increase		203,648,000		1,891,000
c. January 2002 pay increase		203.648.000		5,520,000
d. One day more pay		203.648.000		783,000
e. Payment for centrally furnished services		120.629.000		12,063,000
f. Increased cost of laboratory supplies, materials, and other expenses		238,853,000		6,805,000
Subtotal				30,789,000
2. Research Management and Support:				
a. Within grade increase		70,189,000		1,284,000
b. Annualization of January 2001 pay increase		70,189,000		652,000
c. January 2002 pay increase		70.189.000		1,902,000
d. One day more pay		70.189.000		269,000
e. Payment for centrally furnished services		16.441.000		1,644,000
f. Increased cost of laboratory supplies, materials, and other expenses		49,768,000		1,418,000
Subtotal				7,169,000
3. Cancer Prevention and Control:				
a. Within grade increase		46,733,000		855,000
b. Annualization of January 2001 pay increase		46,733,000		434,000
c. January 2002 pay increase		46,733,000		1,267,000
d. One day more pay		46.733.000		180,000
e. Payment for centrally furnished services		17.775.000		1,778,000
f. Increased cost of laboratory supplies, materials, and other expenses		65,299,000		1,860,000
Subtotal				6,374,000
Subtotal, Built-in				44,332,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes--continued

CHANGES	2001 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,176	$1,192,927,000	238	$203,534,000
b. Competing	1,241	441,964,000	(46)	1,975,000
c. SBIR/STTR	330	76,000,000	24	9,120,000
Total	4,747	1,710,891,000	216	214,629,000
2. Centers	92	258,658,000	7	31,220,000
3. Other research	728	285,533,000	34	24,552,000
4. Research training	1,600	62,100,000	0	6,210,000
5. Research and development contracts	151	261,950,000	8	35,875,000
Subtotal, extramural				312,486,000
	FTEs		FTEs	
6. Intramural research	1,908	563,130,000	0 57	25,524,000
7. Research management and support	783	136,398,000	24	8,517,000
8. Cancer prevention and control	459	456,268,000	14	48,416,000
9. Construction	0	3,000,000	0	0
Subtotal, program		3,737,928,000		394,943,000
Total changes	3,150		95	439,275,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease	Percent Change
Total compensable workyears:				
Full-time employment	3,150	3,245	95	3.0
Full-time equivalent of overtime and holiday hours	13	13	0	0.0
Average ES salary	$130,123	$133,376	$3,253	2.5
Average GM/GS grade	11.2	11.2	0.0	0.0
Average GM/GS salary	$62,753	$65,045	$2,292	3.7
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$67,405	$71,315	$3,910	5.8
Average salary of ungraded positions	$82,330	$87,105	$4,775	5.8

	OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease	Percent Change
	Personnel Compensation:				
11.1	Full-Time Permanent	$158,025,000	$172,332,000	$14,307,000	9.1
11.3	Other than Full-Time Permanent	54,747,000	59,689,000	4,942,000	9.0
11.5	Other Personnel Compensation	12,208,000	13,312,000	1,104,000	9.0
11.8	Special Personnel Services Payments	36,418,000	39,704,000	3,286,000	9.0
11.9	**Total Personnel Compensation**	**261,398,000**	**285,037,000**	**23,639,000**	**9.0**
12.0	Personnel Benefits	59,147,000	64,496,000	5,349,000	9.0
13.0	Benefits for Former Personnel	25,000	27,000	2,000	8.0
	Subtotal, Pay Costs	**320,570,000**	**349,560,000**	**28,990,000**	**9.0**
21.0	Travel & Transportation of Persons	10,043,000	10,947,000	904,000	9.0
22.0	Transportation of Things	1,299,000	1,416,000	117,000	9.0
23.1	Rental Payments to GSA	4,000	4,000	0	0.0
23.2	Rental Payments to Others	6,632,000	7,295,000	663,000	10.0
23.3	Communications, Utilities & Miscellaneous Charges	10,659,000	11,842,000	1,183,000	11.1
24.0	Printing & Reproduction	4,370,000	4,767,000	397,000	9.1
25.1	Consulting Services	17,170,000	19,178,000	2,008,000	11.7
25.2	Other Services	153,636,000	170,483,000	16,847,000	11.0
25.3	Purchase of Goods & Services from Government Accounts	283,867,000	339,202,000	55,335,000	19.5
25.4	Operation & Maintenance of Facilities	74,557,000	79,390,000	4,833,000	6.5
25.5	Research & Development Contracts	269,642,000	303,619,000	33,977,000	12.6
25.6	Medical Care	2,952,000	3,226,000	274,000	9.3
25.7	Operation & Maintenance of Equipment	7,152,000	7,811,000	659,000	9.2
25.8	Subsistence & Support of Persons	0	0	0	0.0
25.0	**Subtotal, Other Contractual Services**	**808,976,000**	**922,909,000**	**113,933,000**	**14.1**
26.0	Supplies & Materials	49,575,000	54,152,000	4,577,000	9.2
31.0	Equipment	33,830,000	37,117,000	3,287,000	9.7
32.0	Land and Structures	14,000	15,000	1,000	7.1
33.0	Investments & Loans	0	0	0	0.0
41.0	Grants, Subsidies & Contributions	2,491,942,000	2,777,165,000	285,223,000	11.4
42.0	Insurance Claims & Indemnities	1,000	1,000	0	0.0
43.0	Interest & Dividends	13,000	13,000	0	0.0
44.0	Refunds	0	0	0	0.0
	Subtotal, Non-Pay Costs	**3,417,358,000**	**3,827,643,000**	**410,285,000**	**12.0**
	Total Budget Authority by Object	**$3,737,928,000**	**$4,177,203,000**	**$439,275,000**	**11.8**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Salaries and Expenses

OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$158,025,000	$172,332,000	$14,307,000
Other Than Full-Time Permanent (11.3)	54,747,000	59,689,000	4,942,000
Other Personnel Compensation (11.5)	12,208,000	13,312,000	1,104,000
Special Personnel Services Payments (11.8)	36,418,000	39,704,000	3,286,000
Total Personnel Compensation (11.9)	**261,398,000**	**285,037,000**	**23,639,000**
Civilian Personnel Benefits (12.0)	59,147,000	64,496,000	5,349,000
Benefits to Former Personnel (13.0)	25,000	27,000	2,000
Subtotal, Pay Costs	**320,570,000**	**349,560,000**	**28,990,000**
Travel (21.0)	10,043,000	10,947,000	904,000
Transportation of Things (22.0)	1,299,000	1,416,000	117,000
Rental Payments to Others (23.2)	6,632,000	7,295,000	663,000
Communications, Utilities and Miscellaneous Charges (23.3)	10,659,000	11,842,000	1,183,000
Printing and Reproduction (24.0)	4,370,000	4,767,000	397,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	15,967,000	17,875,000	1,908,000
Other Services (25.2)	153,636,000	170,483,000	16,847,000
Purchases from Govt. Accounts (25.3)	191,746,000	211,376,000	19,630,000
Operation & Maintenance of Facilities (25.4)	6,960,000	7,737,000	777,000
Operation & Maintenance of Equipment (25.7)	7,152,000	7,811,000	659,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**375,461,000**	**415,282,000**	**39,821,000**
Supplies and Materials (26.0)	49,011,000	53,537,000	4,526,000
Subtotal, Non-Pay Costs	457,475,000	505,086,000	47,611,000
Total, Administrative Costs	**778,045,000**	**854,646,000**	**76,601,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2001 House Appropriations Committee Report Language (H. Rpt.106-645)

Item

Bone Disease -- The Committee encourages NCI to study the role of angiogenesis, the growth of new blood vessels, in the metastasis of breast and prostate cancer to the bone through all available mechanisms, as appropriate, including the development of experimental genetic animal models that replicate the process of human cancer metastasis to the bone and exploring why bone is a preferential site for metastases. (p. 57-58)

Action taken or to be taken

Bone metastasis, or spread of an existing cancer to the bone, is a painful condition that can have a devastating impact on the patient. Recognizing the very real human suffering this condition causes, the NCI is using a multi-pronged approach to the understanding and treatment of bone metastasis. Because angiogenesis, or the development of new blood vessels that feed a tumor, is a crucial step in bone metastasis, NCI is conducting and supporting extensive research into the causes of angiogenesis, as well as ways to reverse the process. Through its research programs, NCI is continuing to expand its understanding of both metastasis and angiogenesis.

Some cancers are particularly likely to spread to the bone. For example, bone metastasis is a frequent complication of breast and prostate cancer patients. The process by which tumor cells spread to the bone is complex, involving a complicated interplay between bone and tumor cells. In a sense, the cancer cells actually conscript the bone to produce chemicals that provide a fertile growth environment for circulating cancer cells. As the basic mechanisms that drive this intricate process are understood, potential points of intervention will be identified as targets for therapy.

Breast and prostate cancer were two of the first cancers in which the role of angiogenesis in the spread of the tumor and survival of the patient was identified. In prostate cancer, increases in tumor angiogenesis have been shown to correlate with tumor spread, and many of the tumor-produced substances that promote tumor angiogenesis, such as the vascular stimulatory molecule vascular endothelial growth factor (VEGF), TGF alpha, and bFGF, are also associated with prostate cancer proliferation, progression, and dissemination. Researchers have also identified a new class of chemokines that play a pivotal role in tumor progression and angiogenesis. In breast cancer, researchers have found that human breast cancer cells carried in immunodeficient mice produce a substance called MCP-1. When the mice are treated with antibodies to MCP-1, survival is extended

and growth of micrometastases is greatly diminished. Any agent that can inhibit the expression or activity of these tumor-derived substances that promote angiogenesis, or inhibit the proliferation and spread of cancer cells, are strong candidates for potential inhibitors of prostate and breast cancer metastases.

To better understand the basic biological mechanisms that facilitate metastasis to the bone, the NCI has actively encouraged the exchange of information, resources, and model systems between members of the research communities of developmental bone biology and of basic cancer biology. A workshop entitled "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities" was convened by NCI staff in November, 2000. The presentations by developmental biologists, cancer cell biologists and clinicians provided a comprehensive picture of the complex extracellular matrix of the bone and identified potential mediators of cancer cell metastasis. The functional differences between human and mouse bone have complicated the development of a reliable model for skeletal colonization, thus new mouse models need to be designed to facilitate both basic and translational research. Current therapies for bone metastasis are directed toward pain control but are not effective in disease treatment. These issues will help focus future planning of research initiatives for the Institute.

Pre-Clinical Research

The Mouse Models of Human Cancers Consortium (MMHCC), launched in September 1999, assembles multidisciplinary teams of scientists who are dedicated to the collaborative development, characterization, and validation of mouse models that are analogs of human cancers. As the MMHCC progresses, NCI will ensure inclusion of additional partners from the academic and private sector research communities through the formation of specialized MMHCC forums. Each individual forum will have a specific focus, for example, genetic technology, prevention models, or site-specific models. In response to opportunities raised in the recent workshop on "Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities", members of the MMHCC will convene a task force to explore the best mouse-modeling and small animal imaging strategies that capitalize on the knowledge base on human cancer bone metastases. This task force will be comprised of experts from basic, translational, and clinical research, and will evaluate the most promising and effective approaches to deriving new mouse models of breast, prostate and other cancers that metastasize to bone.

The NCI is supporting new initiatives in drug development based on the progress made over the last decade in our understanding of the biology of cancer cells. New technology, such as combinatorial chemistry and the miniaturization of assays, will allow for the evaluation of thousands of compounds in a very short time and thereby speed up the process of identifying new candidates for evaluation in clinical trials. Research areas that suggest opportunities 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.

NCI plans to support Interdisciplinary Research Teams (IRT) that will develop new assays, probes, and technologies for molecular target assessment in the development of new agents against specific targets. NCI will support two or more IRTs focused on the development of mechanism-based assays of

antiangiogenic drug activity. The teams will consist of interactive groups of investigators with a broad range of experience in basic angiogenesis research, imaging, cell biology, genetics, pharmacology, pathology, animal models and clinical trials to rapidly evaluate potential surrogate markers of anti-angiogenic activity. These studies will include development of new techniques that will allow us to more effectively image the behavior of angiogenic blood vessels in the body. New array technologies such as "angiochips" will be developed to detect alterations in genes implicated in blood vessel proliferation, in addition to the chip analysis employed to detect genes responsible for angiogenic signals and for the increased affinity of tumor cells for bone or other organs. New bioassays will be developed for detecting both pro- and anti-angiogenic factors in patients' blood or in tumors. These new assays will be studied in breast and prostate cancer animal models as well as in proof of principle clinical trials.

Clinical Research

NCI-supported researchers are investigating and developing novel products that will block angiogenesis. NCI is also supporting research to attempt to improve the effectiveness of existing anti-cancer agents; to develop new agents that inhibit molecular targets or pathways important for the initiation or maintenance of cancer; to develop new agents that inhibit bone invasion by cancer cells; and to develop novel drug delivery systems that target certain organs, such as bone. Some of this work requires the use of newly created genetic model systems – for example transgenic mice that develop prostate or mammary tumors at predictable rates.

To facilitate research into mechanisms of angiogenesis and the development of drugs that target the essential tumor vasculature, NCI recently started the Angiogenesis Resource Center. It is expected that this resource center will significantly aid in the defining of mechanisms controlling tumor angiogenesis and the development of strategies that can disrupt or abrogate angiogenesis and tumor vascularization in both primary neoplasms and metastases that may arise. The Angiogenesis Resource Center's web site (http://dtp.nci.nih.gov/aa-resources/aa_index.html) was activated February 2000, and provides information on the resources available and how to access them.

Item

Breast Cancer -- The development of advanced imaging technologies including medical infrared imaging derived from the U.S. Military and NASA, and other optical and non-invasive modalities which, when converged with emerging treatments such as angiogenic therapy, can be incorporated into comprehensive systems for the early detection and treatment of breast cancer. NCI is encouraged to explore this approach to disease management. (p. 58)

Action taken or to be taken

NCI endorses the concept that the development of advanced imaging technologies holds vast promise of enhancing the early detection and treatment of all cancers. The Institute continues to recognize the great potential that imaging technology holds for cancer and identifies it as an area of extraordinary opportunity. NCI has an array of programs and initiatives aimed at significantly advancing imaging to

more fully exploit its promise for cancer research and care. For the detection of breast cancer in particular, NCI is funding many areas of advanced technology development. These areas include: Digital Mammography, Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), Ultrasound Techniques, Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Optical Technologies (emphasizing the use of the near-infrared region of the spectrum), Elastography, Low-Frequency Electrical Impedance Spectroscopic Imaging, and Microwave Imaging .

Digital Mammography is one of the most promising research areas for improving early detection of breast cancer. Ongoing research in digital mammography includes the development of x-ray source and digital detectors, image optimization and interpretation studies, and studies of impact and cost. Currently, at least four manufacturers have produced digital mammography units for clinical testing and the FDA has approved one of these as being equivalent to conventional film-screen mammography. Although equivalence to conventional mammography has been demonstrated, there is a public health need to determine whether digital mammography is better than conventional film-screen mammography, either in detecting more early breast cancers, or in reducing the number of equivocal results or false positive results.

One imaging factor that can be used to estimate a woman's future risk for breast cancer is the density of breast tissue as seen on mammograms. Increased density indicates a preponderance of glandular tissue over fatty tissue, and appears to be predictive of increased cancer risk. Current research, including a large study of several hundred women, focuses on developing accurate measures of breast mammographic density and correlation of these measures to breast cancer risk. NCI also provides support for a project to develop novel mathematical models that build on known physiological and epidemiological characteristics of breast cancer, along with preliminary information about test performance characteristics and costs to estimate the cost-effectiveness of new and emerging imaging technologies, such as MRI and digital mammography.

The NCI has funded a national multi-institutional network for cooperative studies in diagnostic imaging, called American College of Radiology Imaging Network (ACRIN). For the future, in addition to performing trials originating in academic institutions, this network will develop productive collaborations with industrial sources of new imaging technology and will perform both limited institution pilot studies and full-scale randomized controlled trials to assess the value of imaging innovations in the practice of oncology. Studies in breast cancer will form an important part of the research agenda of this network, aided by collaborative arrangements with the clinical cooperative groups.

NCI believes that it is important to determine whether digital mammography is better than conventional film-screen mammography, and if it is better, what the advantages are. ACRIN has developed a protocol to carry out a large-scale trial designed to help make those determinations and in 2001, ACRIN began a trial of 49,000 women who will receive both digital and conventional mammograms for direct comparison. It is anticipated that the results of this trial will be available within 3 years.

Although Digital Mammography is a promising research area for improving early detection of breast cancer, there is still the need for a concerted effort to overcome the problems of displaying the digital mammograms so that they are accurately interpretable for diagnosis. The current soft-copy (i.e., video) display systems remain an impediment to full realization of the potential of digital mammography. To promote the optimization and interpretation of images from digital mammography systems, NCI issued a Program Announcement (PA) called Development and Testing of Digital Mammography Displays and Workstations. This PA is intended to advance the state of the art in digital mammography displays and workstation design to facilitate clinical acceptance and implementation of digital mammography for improved breast cancer diagnosis. The PA will encourage research and development in three critical areas in digital mammography: Softcopy Display Hardware; Workstation Software and Design; and Image Perception. The first awards involve improvement of monitors, the creation of workstations and their testing in the clinical setting. Of the 18 applications, four are expected to be funded.

NCI is also supporting a multi-center, international clinical trial on the use of MRI in the detection of breast cancer. Nearly 600 patients have been accrued at 14 centers in this trial to test MRI as a tool to decrease the number of false-positive x-ray mammograms that lead to biopsy. NCI is also funding a multi-center trial of breast MRI at six sites as a screening test for breast cancer in women at high-risk for breast cancer.

NCI has funded a 5-year project to test four technologies (MRI-based elasticity imaging, electrical impedance spectroscopy and imaging, microwave spectroscopy and imaging, and near infrared spectroscopy and imaging), which will all be tested in a group of 75 patients arriving for mammography. This project is focused on determining whether one, or a combination of more than one, of these examinations will significantly improve the detection and diagnosis of breast cancer non-invasively.

Related NCI activities include:

$ Exploratory/Developmental Grants for Diagnostic Cancer Imaging: This PA provides support for 2 years of funding at a level adequate for the initial feasibility testing and generation of experimental preliminary data. This program was initiated in 1997, and was reissued for continuation in 2000. These grants fund innovative and creative approaches in diagnostic imaging that lead to new avenues of research, and provide investigators with the initial resources required to accomplish pilot testing of ideas. Since the inception of this ongoing program, 200 applications have been received, and an estimated 53 grants are either currently active. Of those grants, at least 14 are directly involved with research on breast cancer.

$ Novel Technologies for Noninvasive Detection, Diagnosis and Treatment of Cancer: The Unconventional Innovations Program (UIP) seeks proposals that represent the highest potential for revolutionary breakthroughs in the development of technologies to enable the non-invasive sensing of cancer signatures in the living body coupled with capabilities for monitored intervention. These approaches typically carry substantial risk of failing to meet long term objectives. As a result, the NCI issued this request to demonstrate its commitment to explore these high risk approaches. The UIP was specifically soliciting projects to develop technology

systems or systems components to enable sensing of defined signatures of different cancerous or precancerous cell types or their associated microenvironment in the body in a way that is highly sensitive and specific, yet non-intrusive. The highest priority was for systems that can either support or provide a seamless interface between sensing/detection and intervention. Of the five awards that were made in FY 1999, one went to a NASA researcher to develop novel carbon nanotube-based biosensor technology that could lead to detecting molecular signatures of cancer cells, including breast cancer. Three other awards were more targeted towards breast cancer and use either Near Infrared imaging, a Compton Light Source that produces monochromatic high contrast X-rays, or is developing nano-devices as part of a more complex system to sense (and treat) precancerous or cancerous cells in the breast. In September 2000, another project was awarded that targets the development and construction of ultrasound systems to detect cancerous tumors, including breast cancer.

$ Development and Application of Imaging in Therapeutic Studies: This initiative, issued in FY 1999, was designed to support research projects addressing the development and application of labeled therapeutic agents as compounds for imaging studies, and/or the development and application of imaging agents as metabolic markers of response to newly-developed therapeutic agents. Two awards focus on breast cancer. One project is using SPECT imaging to determine the status of drug-resistance in women, and another is using new MR technologies to assess the status of new blood vessels in tumor models, and their response to therapy.

$ Small Animal Imaging Resource Programs (SAIRPs): Small animal models, particularly genetically engineered mice, have become essential discovery tools in cancer research. Small animal imaging techniques are an important tool for providing data about biochemical, genetic or pharmacological processes in vivo, and repetitively in the same animal, without having to sacrifice the animal for analysis. This program, issued in FY 1999 provides shared imaging research resources to be used by cancer investigators, research related to small animal imaging technology, and training for investigators and technical staff in small animal imaging. The initiative was reissued and NCI hopes to fund five more SAIRPs. Although these grants are not focused on a specific type of cancer, the technologies developed will have wide-ranging applications as new animal models, including mouse models of breast cancer, are developed.

$ In Vivo Cellular and Molecular Imaging Centers (ICMICs) and (Pre-ICMICs): In Vivo Cellular and Molecular Imaging Centers were designed to capitalize on the extraordinary opportunity for studying cancer non-invasively, and in many cases, quantitatively due to recent advances in molecular imaging modalities, and molecular and cellular biology. The ICMICs and Pre-ICMICs should facilitate the interaction of scientists from a variety of fields to conduct multidisciplinary research on imaging at the cellular and molecular level. These grants will provide a productive framework within which to expand the capabilities of molecular imaging, which may directly benefit the detection, diagnosis and treatment of breast cancer.

$ Development of Clinical Imaging Drugs and Enhancers (DCIDE): DCIDE is a competitive program to expedite and facilitate the development of promising imaging enhancers (contrast

agents) or molecular probes from the laboratory to early clinical trials. This program is modeled on the NCI-funded RAID program that facilitates development of new therapeutic drugs and biologics. The RAID program will foster the development of target-based therapeutics. Related imaging agents will be necessary for the resultant target-based clinical trials to determine, non-invasively, where and how the target-based therapeutics are performing in patients. The DCIDE program is intended to supply missing steps so that promising discoveries can be translated to the research and clinical environments in the absence of development capacity, clinical connections, or industry interest. The DCIDE program will focus on promising imaging agents that are not otherwise likely to receive an adequate and timely evaluation. The DCIDE program is not intended by itself to provide full-scale clinical development but will facilitate the performance of clinical trials to establish proof of principle of a compelling hypothesis. Once this is accomplished for specific products, it is anticipated that clinical development will continue along established lines under the sponsorship of either private companies or the NCI. Through the DCIDE program, the developer of a promising imaging agent or probe will be given access to the development resources of the NCI to remove the most common barriers between laboratory discoveries and clinical trials. The DCIDE program was publicly announced in June 2000, and the first requests have been submitted, one of which deals specifically with an imaging agent directed at breast cancer.

Item

Childhood Skeletal Malignancies -- . . . . The Committee encourages NCI to enhance the level of scientific knowledge of Osteosarcoma, Ewings sarcoma, and related malignancies affecting connective tissue that often result in limb loss through all available mechanisms, as appropriate, including a consensus conference to develop a research agenda. (p. 58)

Action taken or to be taken

Childhood skeletal malignancy is diagnosed each year in 650-700 children and adolescents younger than 20 years of age. Osteosarcoma (56 percent) and Ewing's sarcoma (34 percent) account for the majority of these bone tumors. Through a series of national pediatric clinical trials conducted by the pediatric oncology cooperative groups over the past three decades, the 5-year survival rate has improved such that more than 70 percent of children with newly diagnosed non-metastatic osteosarcoma or Ewing's sarcoma can expect to survive long-term. Advances in pediatric orthopedic surgery, chemotherapy and radiotherapy have allowed the majority of children with localized disease to undergo limb-sparing procedures as part of their cancer treatment, thus diminishing the long-term impact of their childhood cancer. Approximately 20-30 percent of children is diagnosed with metastatic bone disease and their survival is 50 percent or less. Pediatric oncology researchers and the NCI are committed to learning more about the development of bone malignancies and improving the current treatment modalities to ensure increased survival with diminished toxicity.

Similar research activities supported by the NCI and conducted primarily by researchers associated with the Children's Oncology Group (COG) are ongoing for all of the major types of cancer that

develop in children and adolescents.

Basic Science

A priority of current research efforts is the identification of the molecular biologic characteristics of a patient's diagnostic tumor material that can be used prospectively to predict the tumor's metastatic potential, therapy responsiveness, and the patient's survival prognosis. Patients currently treated on COG clinical trials can be enrolled in a companion biology study that investigates drug resistance related genes, tumor suppressor genes and oncogenes, and other molecular biologic characteristics of the tumor. The goal is to develop a set of biologic prognostic indicators measured at diagnosis that can be used to stratify patients by risk of relapse and to provide a basis for adjustment of treatment intensity. The NCI is also supporting investigations of the molecular biological features of osteosarcoma tumor response to methotrexate, an important chemotherapeutic component, to determine biological factors that may indicate a tumor's likelihood of response or resistance to methotrexate. Gene rearrangements in Ewing's family of tumors are being studied as part of the current Ewing's sarcoma treatment protocol to prospectively assess the prognostic importance of specific tumor gene rearrangements and low levels of tumor cells in the bone marrow at diagnosis.

COG investigators are taking advantage of the extraordinary opportunities available through comprehensive molecular analysis technologies that provide the groundwork for changing the basis of tumor classification from morphological to molecular characteristics. COG researchers successfully competed for 5 years of funding from the "NCI Director's Challenge: Towards a Molecular Classification of Cancer" to use microarray technology to study the gene expression profiles of pediatric sarcomas. This research will examine the genetic characteristics of bone tumors at diagnosis to predict clinical course, treatment responsiveness and survival outcome based on the tumor's individual genetic profile.

Another area of focus for pre-clinical research is the identification of new treatment approaches for osteosarcoma and Ewing's sarcoma. Using an osteosarcoma mouse model, investigators are delivering aerosolized formulations directly to the lungs of either active chemotherapy agents or virus vectors producing immune-system activating cytokines. These studies are designed to determine whether this method of delivering treatment decreases the growth and development of metastatic lung nodules. Investigators plan to translate this approach into a clinical trial for children with osteosarcoma metastatic to the lungs. The COG Bone Tumor Committee conducted a scientific symposium on bone sarcoma biology during the November COG meeting.

Clinical Trials

For osteosarcoma, the COG recently completed a group-wide, randomized prospective trial that examined the impact on outcome of adding ifosfamide and an immunomodulatory agent, muramyl tripeptide, to standard cisplatin, doxorubicin, and high dose methotrexate therapy. Results from this study should be received soon. A nationwide series of pilot studies are now underway to evaluate the use of more intensive alkylator therapy and the adjustment of chemotherapy intensity based on the

degree of histologic necrosis during induction therapy. A subsequent Phase III study will incorporate the concept of increased therapy for patients with an initially inferior response to induction chemotherapy with the chemotherapy regimen to be determined by results from the current pilot studies. Additionally, COG has recently completed a Phase II trial of topotecan in patients with metastatic osteosarcoma to determine the activity of this new agent.

From 1995 to 1998 a group-wide randomized clinical trial for children with Ewing's sarcoma that compared conventional chemotherapy versus a regimen of shorter duration including more intensive alkylating agent dosing was conducted. Results from this study will be reported in the Spring. A new group-wide randomized trial compares conventional chemotherapy to a regimen using chemotherapy interval compression to increase dose intensity of all active agents. COG recently completed a trial investigating the role of high-dose chemotherapy and radiation followed by autologous stem cell reconstitution as consolidation for newly diagnosed patients with high-risk metastatic disease. Results from this study indicate that the high-dose chemotherapy employed did not significantly improve outcome for this high-risk population.

Immunotherapy in the treatment of children with Ewing's sarcoma and the high risk of relapse is being studied using a macrophage activating agent, liposome-encapsulated muramyl dipeptide (ImmTher). This stimulates the pulmonary immune system to destroy tumor cells. The biologic response modifier is given to high-risk patients after completion of surgery, chemotherapy, and radiotherapy in an attempt to prolong disease-free survival by enhancing immune surveillance in the most common site of relapse. As a part of this effort, investigators are exploring the impact of the immunomodulatory therapy on cytokine production, immune cell killing activity and tumor related growth factor levels (VEGF) in the child treated for advanced Ewing's sarcoma.

Numerous Phase I studies are available to children with osteosarcoma and Ewing's sarcoma whose tumors have recurred despite standard therapy. Agents under evaluation are gemcitabine, continuous infusion topotecan, vinorelbine, docetaxel, dolostatin, irinotecan/cisplatin combination therapy, fenretinide, and ET-743. Phase I trials of molecularly targeted agents ZD1839 (EGF receptor) and SU6668 (VEGF receptor inhibitor) will open in the coming year.

A planning meeting for future clinical trials in osteosarcoma was held during the American Pediatric Hematology and Oncology meeting in September. In addition, the COG Bone Tumor Committee met in November to discuss clinical research plans for bone tumors.

While children with these tumors have benefited from the historically high level of participation in clinical trials, the gains in survival outcome by adolescents and young adults with malignancies such as osteosarcoma and Ewing's sarcoma has been less dramatic. COG and the NCI have begun an Adolescent-Young Adult (AYA) Initiative to increase clinical trial participation by this patient population. A first step of the initiative has been to extend the age eligibility for COG osteosarcoma and Ewing's sarcoma clinical trials to 50 years and allow the adult cooperative groups to enroll their patients with bone malignancy.

Identifying Causes of Cancer in Children

The NCI is currently supporting planning and pilot studies to evaluate the feasibility of developing a central registry of cancer cases occurring among children in the United States; building upon the patient population presented to COG institutions. The primary objective in establishing a central registry of childhood cancer cases would be to establish a resource to support and facilitate the conduct of scientific studies of the highest merit and identify environmental and other causes of childhood cancer. A national effort and resource is essential. Single institutions or even consortia of institutions within a limited geographic region see insufficient numbers of cases of childhood cancer to mount definitive studies.

Long-Term Effects of Therapy

The NCI supports research activities to improve the health status of survivors of childhood cancer. The NCI-supported Childhood Cancer Survivorship Study (CCSS) has established a cohort of 14,000 survivors of childhood cancer who were initially treated between 1970 and 1986. The CCSS cohort includes 957 5-year survivors of osteosarcoma and 560 5-year survivors of Ewing's sarcoma. The CCSS is ascertaining key outcomes that are important to survivors of childhood cancer, including heart and lung problems related to their cancer therapy, fertility, health status of offspring, and risk of second cancers. Information from the CCSS can be used to advise survivors of appropriate health-related behaviors and can be used to identify the need for new treatments to avoid deleterious long-term consequences of therapy. The CCSS, initially funded in 1993, is currently in its second 5-year period of funding and continues its important monitoring and research activities for the childhood cancer survivors.

Recent Accomplishments

In the past year, NCI intramural investigators have reported that individuals with Ewing's sarcoma were more likely to have inguinal hernia than those without the cancer. This suggests a disruption in normal embryological development; possibly due to genetic susceptibility or intrauterine exposure, such as viral infection. To further explore this, we are evaluating the possibility of viral infections as a risk factor for Ewing's sarcoma. Also being evaluated is the occupational exposures of parents of individuals who develop Ewing's sarcoma.

NCI intramural investigators have recently collected new information from a group of patients who have survived retinoblastoma. They continue to demonstrate an excess of bone sarcoma, predominantly osteosarcoma, soft tissue sarcomas, and melanoma. We are clinically evaluating the families of the patients with melanoma, who often have sarcomas, to try to detect clinical or genetic markers that could predict risk of second cancers. These patients also have a high frequency of leiomyosarcomas which occur in blood vessels, the gastrointestinal tract, or the uterus. We hope to genotype the individuals with second cancers, to evaluate whether specific variations in the retinoblastoma gene predict risk of second sarcomas or melanoma.

Item

DES Education **--** . . . . The Committee urges NCI to review this plan within a reasonable timeframe and collaborate with CDC on its implementation. The Committee also urges NCI to ensure that public information pamphlets developed by NCI are readily made available to consumers. (p. 58)

Action taken or to be taken

NCI and CDC are collaborating to develop a national campaign to inform American women about the potential health effects associated with Diethylstilbestrol (DES) exposure. Focus groups are being conducted to determine informational and supportive needs. Using information from the focus groups, communication materials will be developed and tested, and in FY 2002, the campaign will be launched with materials disseminated through CDC's networks and NCI's Cancer Information Service to health care professionals, advocacy groups and the public.

DES National Education Campaign: Prescribed for pregnant women to prevent miscarriages, DES, a synthetic estrogen, was subsequently linked to increased risks of cancer, genital abnormalities, and/or compromised fertility. Pregnant women who took the drug between 1938 and 1971, and their children, are at risk--an estimated 5 to 10 million individuals. Although previous DES educational efforts have reached many persons exposed to DES, the knowledge most people have about DES is old and inaccurate. Neither patients nor their health care providers have current information about DES health risks--indicating a need for ongoing screening and health monitoring.

The DES National Education Campaign is designed to fill the knowledge gap by targeting audiences who are predisposed to learning about DES: persons who are aware of their DES exposure status, but are unaware of on-going and new risks; individuals who are unaware of their exposure status, but are experiencing symptoms consistent with DES; persons within the age cohort of DES exposed who are active health-information-seekers; and health care providers who treat DES exposed patients. The campaign employs a "push-pull" strategy, educating patients and providers simultaneously, so that informed consumers will find up-to-date and motivated providers to monitor their health.

The campaign will integrate DES education into on-going and sustainable channels and institutions. Plans include incorporating DES messages into educational materials distributed to persons concerned about associated symptoms such as breast cancer and infertility. The DES National Campaign has partnered with health care professional organizations and patient advocacy groups to develop links between campaign efforts and existing forums for health education. The national campaign will complement traditional educational channels with new electronic media. Campaign evaluation will monitor message penetration, measure the integrated impact of provider and patient campaigns, and use assessment information to take action necessary to maximize campaign influence. The campaign calls for careful integration of research, campaign design, and assessment to determine the most effective and efficient means of reaching affected individuals.

DES Workshop

NCI held a workshop at NIH in July 1999 (DES Research Update 1999, Current Knowledge, Future Directions) as a follow-up to a workshop held in 1992 (NIH Workshop on Long-Term Effects of Exposure to Diethylstilbestrol). The 2-day workshop involved about 175 participants, including academic researchers, government scientists (from NCI, NIEHS, and other NIH Institutes and Offices, the CDC, and the DHHS Office on Women's Health), and DES advocates and organizations. The purpose of the meeting was to disseminate information acquired from ongoing DES projects, to evaluate activities and achievements associated with recommendations from the previous workshop, to identify unmet research and data needs, and to discuss potential opportunities for further research. The agenda included overview sessions on basic laboratory research, epidemiological studies, clinical research, and education and outreach research and activities focused on DES. Breakout sessions in these areas included discussions of the current and future needs for DES-related research and recommendations for addressing those needs. A poster session provided an opportunity to discuss recent research findings and also encouraged the participation of younger researchers. The proceedings of the workshop have been published and are currently available through the Cancer Information Service (1-800-4-CANCER). The complete text of the proceedings is available online at: http://osp.nci.nih.gov/whealth/DES/index.html.

NCI hosts and maintains a website for the medical and lay community to access current information on the health status of DES-exposed mothers, daughters and sons. The website contains helpful hints on talking about DES, which serves as a useful resource for families exposed to DES. The DES publication website is located at: http://dccps.nci.nih.gov/ASRB/pubs/DES_Pubs/directory.html.

Item

Endometrial and Cervical Cancer -- The Committee encourages NCI to conduct a programmatic review of the research portfolios in endometrial and cervical cancer and enhance research in areas of discovery that are not currently being funded through all available mechanisms, as appropriate, including requests for applications for SPOREs. (p. 58)

Action taken or to be taken

In May 2000, NCI, together with DoD, the PHS Office of Women's Health, the NIH Office of Research on Women's Health, the Gynecologic Oncology Group, and the Society of Gynecologic Oncologists, sponsored a retreat on translational research in gynecologic cancer. This 3-day meeting, attended by more than 150 scientists, clinical researchers, and federal program staff, identified areas of scientific opportunity in gynecologic cancer.

NCI established a Progress Review Group (PRG) in early FY 2001to assist in setting long-term priorities for research on gynocological cancers, including endometrial, cervical, and ovarian cancers. Like other review groups, this group is composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a

national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion by the end of FY 2001and NCI will develop an implementation plan by mid FY 2002.

The NCI also recognizes the need to enhance translational research in endometrial and cervical cancers. It is the intent of the NCI to continue to support multidisciplinary translational research on gynecological cancers including those of the endometrium and cervix. Applications for gynecological cancer SPOREs will be accepted for February 1, 2003. Applicants will have an opportunity to resubmit applications every February 1st of each year after this first submission date in 2003. Awards will be made based on the scientific merit of the applications and the availability of funds to the SPORE program.

Item

Esophageal and Stomach Cancer -- Approximately 34,000 Americans will be diagnosed this year with esophageal or stomach cancer and approximately 25,000 will die from these diseases. Both cancers disproportionately affect minority populations, particularly African-Americans and Hispanics. The Committee encourages NCI, in collaboration with NIDDK, to enhance efforts in this area. (p. 58)

Action taken or to be taken

There has been an increase in these tumors and the discovery of interrelationships among gastroespohageal reflux disease, Barrett's esophagus, and adenocarcinoma of the lower esophagus. Thus, NCI has initiated a series of meetings with leading gastroenterology professional groups (e.g., American Gastroenterology Association, American College of Gastroenterology) and the National Institutes of Diabetes and Digestive Diseases (NIDDK), to begin several important activities. First, an NCI-NIDDK Barrett's Working Group has been formed and is reviewing both Institutes' research portfolios relating to Barrett's-associated cancer etiology, prevention, and treatment. The Working Group will consider what is known about the risk factors, what is still unknown, and what research is indicated. Following this review, we have scheduled a series of meetings to examine research opportunities and obstacles, and to stimulate targeted funding initiatives. In September 2000, NCI participated in an Interagency Coordinating Committee Meeting on Barrett's Esophagus that included representatives from NIDDK (lead), the Veteran's Administration, Department of Defense, Centers for Disease Control and Prevention, and Federal Drug Administration. Discussed was a full-scale workshop out of which initiatives in this area could be developed. The utility of an awareness/education program was also discussed.

This activity is a prelude to a formal NCI-initiated Progress Review Group (PRG) focused specifically on esophageal and stomach cancer scheduled for Fall 2001 and charged with assisting in the setting of priorities for research on stomach and esophageal cancers. Like other PRGs, such as those already convened for prostate, breast, colorectal and brain cancers, this PRG will be composed of 20-30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's

current research program as a baseline, the PRG will identify priority areas for research and will issue a final report listing research priorities and resource needs. The report is scheduled for completion in 2002.

Item

Lung Cancer Screening --. . . . The Committee encourages NCI to examine these technologies and their usefulness in early diagnosis and patient treatment. (p. 58)

Action taken or to be taken

Lung cancer is the most common cause of cancer death among men and women. Historical data suggests that patients with surgical early Stage I disease may have 10 year survivals up to 80 percent. This has formed the rationale for early lung cancer detection programs.

Observational trials in the United States and Japan using low dose helical computed tomography (ct) have shown promising results with the detection of early stage disease. These data have been interpreted to suggest great potential for realizing surgical cure and reducing lung cancer-specific mortality. NCI provided funding for the Early Lung Cancer Action Project (ELCAP) trial at Weill Cornell Medical School, and is currently funding another, larger observational trial at Mayo Clinic. It remains to be seen whether these outcomes represent true mortality reductions or are merely the expression of lead-time, length, and over-diagnosis biases inherent in screening. Lead-time bias is the apparent improved survival that results from detecting a cancer earlier and does not necessarily mean that the individual's overall life span has been increased. Length bias is the apparent improved survival that occurs if screening preferentially detects slow-growing, non-aggressive cancers. Many experts believe that a randomized, controlled trial is necessary to answer these questions. The NCI-funded Prostate, Lung, Colorectal and Ovarian (PLCO) study is currently determining whether a randomized, controlled study is possible. The issue is whether high-risk individuals will agree to participate in a randomized controlled study where the experimental group receives screening with spiral CT studies and the control group receives screening with routine chest films.

In parallel with the investigation of contemporary image-based screening methods, modern techniques have made it possible to detect biomarkers in extraordinarily small quantities from blood, sputum, urine, and tumor tissue. Some biomarkers appear to predate the clinical presentation or diagnosis of lung cancer, providing the opportunity to halt or reverse the progression to overt malignancy with life-style modifications, chemoprevention, or molecularly targeted therapy. Tissue and other specimens obtained from high risk individuals undergoing lung cancer screening would provide a valuable bank from which to apply and validate biomarkers that may be useful in other pilot projects. The ultimate goal is to identify biomarkers to enable in the prediction of lung cancer and the definition of high-risk cohorts in whom prevention and intervention are appropriate.

Based on those reasons above, the NCI-funded American College of Radiology Imaging Network (ACRIN) will begin a multi-center, randomized controlled trial of 7,000 individuals at high risk for lung

cancer to determine: whether lung cancer screening with low-dose helical CT reduces lung cancer-specific mortality, and to develop a tissue bank from individuals with pathologically-proven lung cancer that can be used to test biomarkers for lung cancer. ACRIN will collaborate with the NCI-funded lung SPORE programs, and the Early Detection Research Network (EDRN), to develop the biorepository aspect of the randomized spiral CT study.

NCI also issued an RFA in FY 2000 to create a database of spiral CT studies as a research resource for the entire research community. Fifteen applications were received and will be reviewed shortly. It is anticipated that a consortium of approximately five institutions will be created from these applications. The consortium will define guidelines for creating, populating and accessing the database, which will be publicly available over the Internet. The resources would be used by investigators to develop software programs that can automatically find abnormalities or assess their likelihood of malignancy. NCI also supports several individual projects related to the interpretation or evaluation of lung cancer spiral CT screening studies.

Item

Lymphoma -- The Committee understands that NCI is committed to conducting a progress review group on lymphoma. This will give NCI and other Federal agencies the opportunity to evaluate current research and determine future needs. The Committee requests that the Director of the Institute be prepared to provide a progress report at the fiscal year 2002 appropriations hearing. (p. 58-59)

Action taken or to be taken

In August 2001, NCI established a Progress Review Group (PRG) to assist in setting long-term priorities for research on leukemia, lymphoma, and myeloma cancers. Like other PRGs, this one is composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG is identifying priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion by the spring of 2001 and NCI will develop an implementation play by the end of FY 2001.

Lymphomas are cancers that develop in the immune system, the part of the body that protects us from cancer and infection. The immune system includes the bone marrow, spleen, thymus, lymph nodes, and a network of thin tubes that carry lymph and white blood cells. These tissues and organs produce the white blood cells that fight infection and cancer. Lymph nodes are filters that stop infectious agents from spreading and are located in key locations such as the intestine and the lungs. Therefore, when lymphoma occurs, it develops in the very system designed to protect us against disease.

There are two major types of lymphoma -- Hodgkins's lymphoma and non-Hodgkin's lymphoma. Hodgkin's lymphoma (also called Hodgkin's disease) is an uncommon lymphoma which accounts for

less than one percent of all cases of cancer in the U.S. Both types of lymphomas can occur in adults and children.

Both Hodgkin's disease and non-Hodgkin's lymphoma occur with increased frequency among persons infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. In particular, the intermediate- and high-grade types of non-Hodgkin's lymphoma are more common among persons with HIV/AIDS. In HIV-infected patients, about one-half of all B-cell lymphomas are associated with the Epstein-Barr virus, including virtually all primary central nervous system lymphomas in patients with AIDS. Additionally, the human T-lymphotropic virus 1 is associated with lymphomas and leukemias. Hepatitis C virus is associated with a particular type of lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma of the gastrointestinal tract. Decreased immune function, whether it results from exposure to certain viruses or from other exposures, clearly puts some people at higher risk than others.

While it is hoped that understanding the demographics and trends of lymphoma will suggest clues to the etiology of the cancers, identifying causes and risk factors associated with lymphomas has remained a formidable challenge to investigators. This is due, at least in part, to the fact that the various sub-types of these tumors behave differently from one another. With the observed increasing incidence rates in the U.S. Population, lymphoma research that examines the role of environmental factors is of particular interest to the Institute. For example, herbicides and other chemicals may increase the risk of these diseases.

NCI's Surveillance of Lymphoma

Taken together, Hodgkin's disease and non-Hodgkin's lymphoma are the fifth most common type of cancer diagnosed and the sixth most common cause of cancer death in the U.S. Whereas most cancer rates have been declining in the 1990's, rates for lymphoma have risen for reasons that are not clear.

The magnitude of the burden imposed by lymphoma and trends in this burden are being tracked by the NCI's Surveillance, Epidemiology and End Results (SEER) Program. Non-Hodgkin's lymphoma is much more common with 54,900 cases diagnosed in 2000 as compared to 7,400 cases of Hodgkin's disease. The 1-year survival rates for Hodgkin's disease and non-Hodgkin's lymphoma are 93 percent and 70 percent, respectively, with 5-year survival rates 82 percent and 51 percent, respectively. An estimated 27,500 Americans died of lymphoma in 2000.

NCI Sponsored Research on Lymphoma

NCI supports a large research project portfolio related to lymphoma comprised of over 400 individual projects, totaling over an estimated $82 million for lymphoma, Hodgkin's and non-Hodgkin's, research in FY 2000. In addition NCI sponsors a very large number of lymphoma cancer clinical trials by grants to individual investigators in hospitals and academic institutions, by grants to cancer centers and large multi-center research consortia, by collaboration with pharmaceutical and biotechnology firms, and within its intramural programs. There are currently 436 clinical trials in lymphoma of which 299 are NCI sponsored.

NCI's scientific investment in cancer genetics has already paid huge dividends. The Cancer Genome Anatomy Project (CGAP) has resulted in the cataloging of tens of thousands of human and mouse genes. New technologies have permitted scientists to determine which genes are expressed (active) in normal and cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as environmental agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public databases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome.

NCI has a concerted effort underway to understand the genetic basis of lymphoma. Currently, there are four cDNA libraries in CGAP from lymphoma and three from normal lymph node tissue. Although one of CGAP's aims is to discover genes important to our understanding of cancer development, an important outcome has been the rapid rate of contribution by CGAP to gene discovery overall. CGAP is currently the prime depositor of sequences into the public Expressed Sequence Tag (EST) database. Sequencing from lymphoma and normal lymph node libraries has generated over 62,000 sequences representing nearly 14,000 genes. Sequences from nearly 1,200 unknown unique genes from lymphoma have been entered into the CGAP database.

The CGAP database is a unique resource that allows scientists to develop tools to perform large-scale genomic analyses to characterize tumors genetically. This genetic characterization can help explain why patients diagnosed with the same cancer differ dramatically in their responses to treatment. For example, a collaboration of scientists (including NCI scientists) genetically analyzed diffuse large B-cell lymphoma, an aggressive cancer that is the most common type of non-Hodgkin's lymphoma. For 40 percent of patients with this diagnosis, standard multi-agent chemotherapy is curative. A compelling clinical problem is to understand why the remaining 60 percent of patients succumb to this disease despite chemotherapy. Reasoning that the varying therapeutic responses of patients with diffuse large B-cell lymphoma are due to undefined molecular differences in their tumors, DNA microarray technology was used to define the gene expression profiles of diffuse large B-cell lymphoma samples on a genomic scale. This new technology is capable of measuring the activity of tens of thousands of genes at the same time, thus creating a molecular portrait of the cells being studied.

For this study, the CGAP was used to create a specialized DNA microarray, the Lymphochip, that is enriched in genes that function in normal and malignant lymphocytes. Lymphochip microarray analysis of gene expression in diffuse large B-cell lymphoma samples revealed that this single diagnosis actually contains two different diseases that differ in the expression of hundreds of genes. The two types of diffuse large B-cell lymphoma that were discovered each resemble a different type of normal B lymphocyte, suggesting that these cancers have distinct cellular origins. Clinically, patients with these two types of diffuse large B-cell lymphoma had strikingly different responses to chemotherapy. Patients with one lymphoma subtype, termed germinal center B-like diffuse large B-cell lymphoma, had a favorable prognosis: 75 percent of these patients were cured by chemotherapy. Patients with the other lymphoma subtype, termed activated B-like diffuse large B-cell lymphoma, had a poor response to

chemotherapy with less than one quarter of these patients achieving a long term remission. This study provides a clear demonstration that genomic-scale gene expression analysis can define clinically important subtypes of human cancer. In the future, such gene expression profiling of cancer cells will be used to guide patients towards therapies that are tailored for their particular diseases.

At the molecular level the genetic lesions associated with or contributing to the etiology of lymphoma are chromosomal translocations causing aberrant patterns of proto-oncogenes normally expressed, or the expression of proto-oncogenes not normally expressed, in lymphoid cells. These genes are generally in the family of transcription factors, which are proteins required for gene expression. In addition, scientists also have identified a unique family of proteins, which suppress programmed cell death, or apoptosis, and contributes to the development of some lymphomas. The aims of NCI's research projects are highly diverse and are designed to understand the molecular lesions relevant to the pathogenesis of lymphomas; understand the role of Epstein-Barr virus in malignant diseases; develop potentially novel approaches to cancer therapy by targeting viral genes or genetic abnormalities; develop chemotherapeutic regimens designed to achieve cure in patients with lymphomas, while minimizing toxicity; define risk groups using clinical and biological parameters; and promote the utilization of the overall expertise in lymphoid malignancies at NCI for the benefit of patients with lymphomas. The NCI has supported and continues to support many basic and clinical research programs that are attempting to better characterize the immunology and biology of lymphomas, and to increase the potential for cure of these patients. Studies in non-Hodgkin's lymphoma have suggested that a defect in programmed cell death, or apoptosis, is critical to the development of lymphomas. An increasing number of genes related to this process have been identified.

Another component of the research portfolio is the viral etiology and biology of lymphoid malignancies in humans. Current research focuses on understanding the role of viral genes in the initiation and progression of viral-associated lymphomas to provide the basis for future investigations on treatment strategies. Specifically, NCI supports basic research on both human and animal DNA and RNA containing viruses that are known etiologic factors and/or cofactors in the initiation and progression of lymphoid malignancies. One reason for the rising rates of lymphomas has been the HIV/AIDS epidemic. A new Program Announcement in collaboration with NIDCR, Epidemiology of HIV-Associated Cancers, emphasizes an interest in research on viruses associated with the development of lymphomas in persons who are HIV-infected.

Treatment of Lymphoma

There have been major advances in the therapy of patients with lymphomas, especially the non-Hodgkin's lymphomas. NCI currently sponsors 75 clinical trials related to adult Hodgkin's disease (of 106 listed in the NCI's PDQ data base) and 25 clinical trials for childhood Hodgkin's disease (of 39 in PDQ). NCI also sponsors 133 clinical trials related to adult non-Hodgkin's lymphoma (of 192 in PDQ) and 37 for childhood non-Hodgkin's lymphoma (of 59 in PDQ). Another 29 NCI-sponsored clinical trials relate specifically to AIDS-related lymphomas (of 40 in PDQ). These trials are aimed at improving treatments for lymphomas. Additional funds are also devoted to patient accrual for studies within the cooperative group setting.

Three types of treatment are most commonly used for lymphomas: radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells and shrink tumors); chemotherapy (using drugs to kill cancer cells and shrink tumors); and immunotherapy (treating cancers with monoclonal antibodies or vaccines). To treat certain types of non-Hodgkin's lymphoma that spread to the brain, chemotherapy may be put into the fluid that surrounds the brain through a needle in the brain or back (intrathecal chemotherapy).

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

The NCI is involved in the development of a large number of new chemotherapy agents with unique mechanisms of action. Drugs which induce apoptosis, or programmed cell death, include compound 506U78, a purine analogue which has demonstrated impressive activity in a variety of lymphoid malignancies, even after failure from bone marrow transplantation, retinoids, and arsenicals. Other agents inhibit the cell cycle including UCN-01, rapamycin, and flavopiridol, or inhibit expression of normal genes through histone deacetylation, such as depsipeptide. Proteosome inhibitors and antiangiogenesis agents are also in clinical trials.

Perhaps the most important new treatment approaches involve the increasing number of biological therapies. Biological treatment tries to help the body to fight cancer or infections. It uses materials made by the body or made in a laboratory to boost, direct, or restore the body's natural defenses against disease. The most widely studied biological therapies have been the monoclonal antibodies. The NCI is collaborating with pharmaceutical sponsors in further development of rituximab by sponsoring several trials which will further elucidate the role of this antibody in the treatment of patients with various forms of non-Hodgkin’s lymphoma and Hodgkin’s disease. For example, trials are underway in indolent and aggressive non-Hodgkin’s lymphoma that are combining the antibody with chemotherapy as well as with other antibodies, attempting to attack multiple therapeutic targets on the same tumor cell. In addition, NCI-sponsored studies are evaluating newer antibodies including Zevalin, Hu1D10, and epratuzumab. Zevalin is an anti-CD20 radioimmunoconjugate which has the potential advantage of being able to carry radioactivity directly to the tumor site where it kills not only the antigen positive tumor cells, but also cells which may be antigen negative or those which in an area of the tumor which chemotherapy does not penetrate well. These radioactive antibodies are being evaluated at low doses as well as higher doses to be used in the setting of bone marrow transplantation.

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

evaluating how those signaling events correlate with clinical response to antibody therapy or the development of drug resistance.

More than 80 percent of patients with follicular non-Hodgkin's lymphoma over-express the bcl-2 gene. The product of this gene inhibits apoptosis of the malignant lymphocytes which causes the tumors to grow and to be resistant to chemotherapy agents. A new anti-sense compound is in clinical trials which has bcl-2 as its target. Preliminary data suggest that it may be particularly effective when combined with chemotherapy.

Bone marrow transplantation and peripheral blood stem cell transplantation are also being tested in clinical trials for certain patients. NCI spends nearly $70 million per year on transplantation research (relevant to numerous cancers in addition to lymphomas). Sometimes Hodgkin's disease becomes resistant to treatment with radiation therapy or chemotherapy. Very high doses of chemotherapy may then be used to treat the cancer. Because the high doses of chemotherapy can destroy the bone marrow, marrow is taken from the bones before treatment. The marrow is then frozen, and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer. The marrow is then thawed and given back to the patient through a needle in a vein to replace the marrow that was destroyed. This type of transplant is called an autologous transplant. If the marrow is taken from another person, the transplant is called an allogeneic transplant. Another type of autologous transplant is called a peripheral blood stem cell transplant. The patient's blood is passed through a machine that removes the stem cells (immature cells from which all blood cells develop), and then returns the blood to the patient. This procedure is called leukapheresis and usually takes 3 or 4 hours to complete. The stem cells are treated with drugs to kill any cancer cells and then frozen until they are transplanted to the patient. This procedure may be done alone or with an autologous bone marrow transplant.

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

Allogeneic bone marrow transplant may cure patients who do not respond to standard chemotherapy. However, the mortality of this procedure in patients with lymphomas has been very high. There has now been an expanded information base on the use of non-myeloablative transplants with donor leukocyte infusions in non-Hodgkin's lymphoma. Investigators from the Fred Hutchinson Cancer Center have described their experience with patients over the age of 55 years. Graft-versus-host disease occurred less frequently than expected and many patients were able to go through the procedure without requiring hospitalization. As a consequence, the notion that more intensive treatment is better is being challenged and the role of the immune system in cancer progression is being better delineated.

Anti-cancer vaccines are a high priority of research for NCI. Vaccine therapy for lymphomas has shown considerable promise. In an attempt to export this technology as rapidly as possible, the NCI is sponsoring a multi-institutional trial in which patients will get standard treatment for their lymphoma followed by vaccine or no additional treatment.

Item

Marine Mammals Research -- Sharks, skates, and rays seem to have an unusually low incidence of cancer and the potential for bioactive molecules to inhibit disease process in humans. The Committee encourages NCI to study the immune systems and bioactive cell and tissue molecules of these marine animals to understand their resistance to cancer and the potential development of more effective therapies to inhibit cancer in humans. (p. 59)

Action taken or to be taken

In 1992, I. William Lane authored a book entitled, ASharks Don=t Get Cancer,@and later a follow-up publication, ASharks Still Don=t Get Cancer,@ both of which promote shark cartilage to fight malignancies. The alleged benefits of powdered shark cartilage have been widely publicized with claims that it could treat cancer, arthritis, and other diseases. Many companies are now marketing shark cartilage pills, and oncologists are finding that a growing number of their patients have tried this alternative therapy. However, at the April 2000 meeting of the American Association of Cancer Research (AACR) in San Francisco, two researchers presented findings proving that sharks do get cancer. Based on a compilation of tumor cases in the NCI-sponsored Registry of Tumors in Lower Animals, located at the George Washington University (GWU), Washington, D.C., evidence was documented on over 40 benign and malignant tumors in sharks, skates, and rays. These species all belong to the chondrichthyes family, whose members lack a bony skeleton. Dr. John Harshbarger, GWU, and Dr. Gary Ostrander, The Johns Hopkins University, reported that these neoplasms, a third of which are cancers, occur in at least 20 species and originate from 16 cell types in all organ systems except respiratory. Moreover, neoplasia has been found in more primitive cartilaginous fish (lamprey and hagfish) as well as in cartilaginous fish that are more advanced than sharks (lungfish, paddlefish, sturgeon, and bowfin). Especially significant are three tumors of cartilaginous origin, two in dogfish sharks and one in a cat shark.

Research by Dr. Judah Folkman of Harvard University, dating from the 1970s, has found that collagen, a substance found in cartilage, can block the growth of new blood vessels that are essential for tumor growth. In theory shark cartilage might stop cancer by blocking the growth of new blood vessels.

Because of the need to obtain conclusive evidence for or against the benefit of shark cartilage in cancer therapy and the continued strong public interest, the NCI is collaborating with NCCAM to sponsor clinical trials in this area. A Phase III randomized study of induction chemotherapy and radiotherapy, with or without an oral shark cartilage extract, is now in the accrual stage for patients with stage IIIA or IIIB unresectable non-small cell lung cancer. This double-blind, placebo- controlled, multicenter trial is being conducted through the NCI=s Community Clinical Oncology Program with oversight by NCI

Cancer Therapy Evaluation Program. Accrual began in June 2000, with a total of 756 patients to be enrolled in this study. The current study is significantly stronger than the one previously reported in 1998. The latter study consisted of only 47 patients with advanced breast, colon, lung, or prostate cancer who were treated with shark cartilage pills. In that small study, shark cartilage was found to be ineffective. The rationale in this new trial is that shark cartilage extract may help shrink or slow the growth of non-small cell lung cancer cells. It is not yet known if the combination of chemotherapy and radiation is more effective with or without shark cartilage.

An additional Phase III trial has just been approved. This trial will enroll patients who have either breast cancer or colorectal cancer. Since there is no previous evidence that shark cartilage is efficacious for a particular site, stratification by disease site will balance the arms of the study regarding potential discordance of survival across disease sites. Because breast and colorectal cancers are common, accrual should be rapid. One goal of the study, and a secondary endpoint, is to determine if shark cartilage treatments given in addition to standard therapy can improve the quality of life over and above that experienced through standard treatment plus placebo. Accrual of 600 patients is planned.

In addition, NCI provides extensive information for physicians and the public interested in the potential use of shark cartilage for cancer treatment. Information is made available through CancerNet and the Physician Data Query (PDQ) web-based systems.

Item

Molecular Markers -- The development of molecular markers that are predictive of the presence or likelihood of regional metastasis in patients with head and neck cancer would provide useful prognostic information as well as identify patients at risk who could benefit from early elective treatment to the regional lymph nodes. NCI is urged to expand research in this area. (p. 59)

Action taken or to be taken

This Congressional query pertains to the early diagnosis of regional lymph node spread. The single most significant indicator of worse prognosis is spread to the regional lymph nodes. Patients with metastases to regional lymph nodes have about half the 5 year survival as patients without such metastases, for a given size of primary tumor. When nodes are not felt in the examination, or discerned from the CT scan or MRI, they could still contain cancer in a minority of patients. One of the goals of research on molecular characteristics of head and neck cancer, including the assessment of the likelihood of or the detection of occult lymph node metastasis, is the correlation of such molecular characteristics with behavior of the cancer is it likely to spread, to recur, or to be responsive to treatment?

NCI is collaborating with the National Institute for Dental and Craniofacial Research (NIDCR) and the National Institute for Deafness and other Communication Disorders (NIDCD) on projects that address increasing the cure and prevention of head and neck cancer. The objective of one pilot program is to determine the feasibility of exchanging scientific information between NCI and NIDCR program staff on grants of mutual interest in order to improve communication between the institutes on the progress and

opportunities in head and neck cancer research. Since 1996, the NCI has supported multidisciplinary translational research in oral cancer by co-sponsoring, with NIDCR, three Oral Cancer Research Centers (U Alabama, UC San Francisco and U Chicago) with total costs of $5.5 million to the NCI over a period of 5 years.

In February 1999, NCI, NIDCR, and NIDCD held a Priorities Setting Workshop to address barriers, gaps, and opportunities for progress in head and neck cancer treatment and prevention. As a direct response to the deliberations of this workshop, NCI and NIDCR have decided to support the establishment of "SPORES" (Specialized Programs of Research Excellence) in head and neck cancer, beginning in 2002, rather than to renew the oral cancer centers funding. The major purpose of these multidisciplinary SPORES will be to increase translation of the cancer biology basic research into the clinic to improve patient outcomes. Studies on functional preservation of voice and swallowing will also be encouraged. Research in the SPORES will encompass biomarkers, databases, statistics expertise, as well as translational clinical trials for treatment and prevention of this disease.

A tissue repository with clinical and epidemiological data would be very helpful in identifying markers with promise. Such a repository is in the planning stages, with collaboration between NCI and NIDCR. The NCI has also published a comprehensive announcement of current NCI research funding opportunities in head and neck cancers. This announcement can be found at http://www.cancer.gov/disease-initiatives/headneckcancer/main_toc.html.

To further support, translational research NCI issued a program announcement to support pilot studies of novel markers or innovative assays for the early detection, assessment of prognosis, or prediction of response to treatment of cancers.

Molecular approaches are already being piloted for detection, staging and treatment. It is known that up to 90 percent of squamous cancers of the head and neck have abnormalities in the p16/Rb/cyclin D1 pathway, leading to abnormal signals for cells to proliferate. Small studies have associated such abnormalities with a worse prognosis. Patients with head and neck squamous cancers also may have increased expression of vascular endothelial growth factor (associated with angiogenesis, or new vessel formation), and these patients may have poorer survival. Other markers, such as urokinase plasminogen activator, and epidermal growth factor receptor, have also been associated with decreased survival. Comprehensive molecular analysis techniques, such as cDNA arrays, are also being applied to head and neck cancer.

Cooperative group Phase III trials often include the collection of tumor samples in order to study the association of molecular characteristics with prognosis or with response to therapy. An example of this early work is the study of a marker of tumor proliferation (Ki-67) and abnormal expression of p53 in patients with locally advanced head and neck cancer treated with radiation therapy. Although this study failed to define these two markers as prognostic for survival in this large cohort, they provided data that will be useful in planning and carrying out future marker studies.

Fortunately, several pharmacologic agents have now been shown to interact with some of the signaling

cascades thought to be important in the progression and metastases of head and neck cancer, such as EGFR and VEGF. Such agents offer promise to study effects of inhibiting a particular pathway, as well as in combination with treatments that are currently employed, such as radiation and chemotherapy. Several NCI-sponsored trials are currently ongoing with such agents. Head and neck cancer patients often have tumors that can be sampled during therapy to see whether the new drug has affected its molecular target. Recently, NCI has generated a drug development plan for such agents in treatment of advanced and/or recurrent head and neck cancer. If they are promising, then use of targeted therapy could be studied in earlier stage disease. Such early trials will also look at the effect of the drug on the target molecule in the cancer itself, thus leading to definition of a rational dose for such patients.

Intervening in cancer progression at early stages, before the appearance of invasive cancer, is a promising strategy for extending survival in patients with head and neck cancer, who frequently develop with premalignant lesions prior to their cancer diagnosis and who are at very high risk for a re-occurring cancer after their initial curative treatment. The Division of Cancer Prevention is sponsoring multiple chemoprevention trials aimed at preventing progression of such precancerous lesions to overt invasive cancer in the oral cavity, larynx and pharynx. Ongoing studies include several that are assessing the chemopreventive efficacy of various retinoids, a group of drugs that have been shown in prior clinical trials to revert precancerous lesions of the oral cavity and to prevent second primary cancers in patients. Included in this list is a large, Phase III multi-institutional trial of 13-cis retinoic acid versus placebo in over 1300 curatively treated head and neck cancer patients, with the aim of determining if 13-cis retinoic acid reduces the rate of second tumor development in these patients. This trial has completed its accrual. Results from this trial are not yet available, although a recent analysis to reaffirm the safety of this approach revealed no adverse effects in the drug-treated group. Other agents that are being studied in smaller trials are 9-cis retinoic acid, 4-hydroxyphenylretinamide (4-HPR), retinyl palmitate, curcumin, and Bowman-Birk inhibitor. Combination therapies using biological approaches with alpha-interferon, 13-cis retinoic acid, and vitamin E are also being tested in patients with advanced premalignant lesions of the larynx. Promising preventive agents that are being developed include non-steroidal anti-inflammatory agents and lipoxygenase pathway inhibitors, two classes of drugs that appear to interfere with cancer cell growth, have minimal toxicity, and are currently in general clinical (non-cancer) use.

Built into the design of all prevention clinical trials are secondary end points assessing the potential of various markers to predict prognosis, drug efficacy, and to substitute for the endpoints of cancer incidence and survival (surrogates). Identifying and validating such surrogate endpoint biomarkers could replace cancer incidence as the major endpoint and could significantly reduce the time and cost necessary to complete these clinical trials. Examples of biomarkers that are being studied include markers of cell proliferation, oncogene expression, cell cycle regulatory proteins, indices of genetic damage, and differentiation markers. Tissues are being saved from the clinical trials to allow future studies of novel markers as these become available.

Item

Multiple Myeloma -- Multiple myeloma (MM) is an incurable cancer of the plasma cells of the bone

marrow. MM is the second fastest growing hematological cancer in the U.S. The Committee is pleased that MM was included in an NCI progress review group and looks forward to hearing about the Institute's plans for the groups findings at the fiscal year 2002 appropriations hearing. (p. 59)

Action taken or to be taken

In August 2001, NCI established a Progress Review Group (PRG) to assist in setting long-term priorities for research on leukemia, lymphoma, and myeloma cancers. Like other PRGs, this one is composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG is identifying priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion by the spring of 2001 and NCI will develop an implementation play by the end of FY 2001.

Multiple myeloma is a rare cancer of the bone marrow that involves the plasma cells, which play an important role in the body's immune response through the production of antibodies. The disease is related to the lymphomas and at one time was included in the general category of lymphoma. Multiple myeloma is the second fastest growing hematological cancer in the U.S. Common effects of the cancer include bone destruction caused by the plasma-cell tumors, life-threatening bacterial infections, and kidney damage. While there has been progress in managing the effects of the disease, conventional chemotherapy has not been successful in treating the underlying cancer. High-dose therapy with bone marrow transplant is used in the management of patients under age 70. ThalidomideBthe medication that caused severe birth defects when given to pregnant women, is of value in treating these patients because the drug reduces the blood supply to the tumor. Overall, treatment options are limited.

The median age at diagnosis of multiple myeloma is 62 years. There is wide variation in occurrence among U.S. Populations, and the reasons for these differences are unknown. Incidence rates in black men are seven times higher than those in Japanese-American men and more than double the rates of white men. Among women there is a similar pattern of occurrence, with Chinese-American women at lowest risk, black women at highest risk, and white women approximately in the middle of the two. The mortality patterns by race and ethnicity are similar to those for incidence, with blacks having approximately twice the rate of whites. Mortality rates are approximately half those for incidence, underscoring the high mortality associated with multiple myeloma. The average survival has increased only moderately since the 1970's, and is less than 4 years from time of diagnosis.

The etiology of multiple myeloma remains unknown. Possible etiologic factors include ionizing radiation and occupational exposures. Recent epidemiologic studies have failed to support past associations between benzene and multiple myeloma. There is a consistently recognized increase in incidence among agricultural workers. Hormonal influences may also be important, and studies are underway to explore possible genetic links, as well as past history of inflammatory diseases.

While some groups have reported the presence of the newly identified human herpes virus-8 (HHV-8)

in the genetic material of stromal bone marrow cells of patients with multiple myeloma, other European and U.S.-based studies have not always identified the virus. HHV-8 is probably the causative agent of Kaposis's sarcoma, and has also been identified in two other B-cell disorders, primary effusion lymphoma and multicentric Castleman's disease. That multiple myeloma is also associated with B-cell disorders made the link plausible when first reported. Currently, there are questions whether the finding of HHV-8 in these patients suggest a link to development of multiple myeloma. Instead, it is possible that the HHV-8 findings initially reported reflect the underlying incidence of HHV-8 in the populations.

Overt myeloma is often preceded by a disorder known as Monoclonal Gammopathy of Undetermined Significance. A group from the Mayo Clinic is evaluating the prevalence of this entity and is following patients to determine the frequency with which MM develops and the immunological changes that may be associated with this transformation. Therapeutic progress will be enhanced by a better understanding of the biology of a disease. A result would be the availability of therapies which target a specific tumor type. Other investigators from the Mayo Clinic are evaluating a number of genetic alterations in myeloma cells to see how they may influence programmed cell death, or apoptosis. Interleukin-6, or IL-6, is a growth factor for MM cells. The effect of this cytokine on a number of MM signaling pathways is being evaluated using both PCR and cDNA microarray analysis. The goal would be new therapeutic strategies.

Despite initial responsiveness to cytotoxic chemotherapy, patients with MM eventually develop multi-drug resistance. Studies are ongoing at several institutions, including the University of Arizona, which are evaluating newly recognized mechanisms of drug resistance. Using a DNA array analysis, these investigators will be evaluating the effect of genes involved in drug resistance and apoptosis and the effect of resistance modifiers on those genes in myeloma cells. Other targets being explored include those involved in cell adhesion. A group at the University of South Florida seeks to determine how cells survive the initial chemotherapy insult and then go on to develop drug resistance. They are investigating the hypothesis that the myeloma microenvironment may disrupt cellular pathways and influence drug response by conferring cell-adhesion-mediated drug resistance.

BCNU is an agent with demonstrated activity in MM. Unfortunately, cells eventually become resistant due to the activity of a number of DNA repair mechanisms. O6-benzylguanine is a relatively non-toxic drug which has the ability to sensitize cells to cytotoxicity of BCNU in vitro by inhibiting these mechanisms. Phase I and II trials are now underway to determine if the efficacy of BCNU can be increased at standard doses and in the transplant setting.

NCI-sponsored research is also focusing on developing new and more effective chemotherapy agents. One such class of drugs are the farnesyl transferase inhibitors. These drugs prevent the activation of the RAS oncogene, which may be responsible, in part, for the tumor growth. Clinical response rates are being correlated with drug levels and inhibition of farnesyl transferase and mutation status of the RAS gene. Another class of drugs which, while old, are only recently being rediscovered, are the arsenicals. Arsenic trioxide is extremely active in acute promyelocytic leukemia. Other studies have shown that it induces programmed cell death in a variety of lymphoid malignancies. Thus, it is now being tested in patients with MM as well.

High dose chemotherapy with autologous stem cell transplantation has emerged as a standard treatment option for select patients with MM based on the reports of a single French study. An U.S. trial is coming to completion within the next few months that will either confirm or refute these findings. Nevertheless, few, if any, patients are cured with this procedure. As a result, a number of modifications are being evaluated, including the addition of drugs such as thalidomide. Other studies are attempting to modify the patient's own leukocytes to recognize the tumor cells as foreign and to mount an immune response against those cells. Additional studies are determining the feasibility of inducing an active immune response against myeloma-specific antigens, such as MUC-1 and DF3.

Preclinical studies of idiotype immunization demonstrate that this approach can induce an immune response which prevents tumor relapse or progression in myeloma models. Investigators at the Fred Hutchinson Cancer Research Center (FHCRC) are evaluating whether a series of immunizations can induce idiotype specific T cell responses following autologous and allogeneic stem cell transplantation. Once the optimal method of delivering the immunizations is determined, they will evaluate the ability of immunization to induce immune responses in patients with MM following stem cell transplantation.

Allogeneic bone marrow transplantation remains the only potentially curative therapy for MM. The toxicities associated with this procedure in patients with MM have been almost prohibitive, with a 30 percent-50 percent treatment-related death rate. Moreover, age restrictions limit the number of patients who might be eligible for this procedure. There has now been an expanded information base on the use of submyeloabltive transplants with donor leukocyte infusions in MM. Investigators from the FHCRC have described their experience with patients over the age of 55 years. Graft versus host disease was less than expected and many patients were able to go through the procedure without requiring hospitalization. As a consequence, the notion that more intensive treatment is better is being challenged and the role of the immune system in cancer progression is being better delineated.

Many patients fail stem cell transplantation and major efforts are directed at identifying the reasons and to develop methods to improve on these results. Investigators at the Dana Farber Cancer Center are developing anti-myeloma specific T cells to treat minimal residual disease following transplantation. Also, they are developing methods to induce a patient immune response against HHV-8, a recently discovered tumor specific virus.

Another approach to the management of patients who have failed a bone marrow transplantation is the use of donor leukocyte infusions (DLI). DLI include cells which are capable of graft-versus-myeloma effect, however they are also capable of generating a potent graft-versus-host-disease which may be fatal to the patient. Studies of the T-cell repertoire post DLI are being conducted to better define the necessary T-cell population.

Investigators at the University of Arkansas are attempting to improve on the efficacy and safety of DLIs. They are evaluating the clinical effects of infusion lymphocytes transduced with a suicide gene that will permit the lymphocytes to have the beneficial graft-versus-myeloma effect but without the GVHD.

The NCI also funds the International Bone Marrow Transplant Registry which is the world's largest body of data on outcomes following transplantation for myeloma and other tumors. Data is provided from more than 400 centers and there are now data for more than 65,000 transplants world-wide. These data are used for determining transplant regimens for specific clinical situations, identifying prognostic factors, comparing transplant regimens, comparing transplant with non-transplant approaches, evaluating cost and cost-effectiveness, planning clinical trials, and developing approaches to evaluate patient outcome.

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

The NCI remains committed to improving the outcome of patients with MM through funding basic and clinical research projects. The Cancer Therapy Evaluation Program funds 28 grants which involve MM with a total budget of more than $20 million.

Item

Multiple Myeloma -- The Committee continues to urge NCI to support epidemiological and other data gathering activities relevant to MM and to coordinate efforts with CDC, NIEHS, the Office of Rare Diseases, and the Office of Research on Minority Health. The Committee encourages the Institute to disseminate and educate the public and health professionals about the symptoms of and treatment for MM. (p. 59)

Action taken or to be taken

Please refer to pages NCI-62 through NCI-65 of this document for NCI's response to this significant item regarding Multiple Myeloma.

Item

National Occupational Research Agenda -- The Committee encourages NCI to work with the National Institute for Occupational Safety and Health to enhance research in relevant National Occupational Research Agenda priority areas such as Cancer Research Methods, Special Populations at Risk, Mixed Exposures, Risk Assessment Methods, and Exposure Assessment Methods. (p. 59)

Action taken or to be taken

For almost 25 years, NCI has collaborated with the National Institute for Occupational Safety and Health (NIOSH) on research projects related to occupational health issues. In FY 2001, NCI

collaborated with NIOSH on several research activities that support the initiatives of the National Occupational Research Agenda (NORA); and NCI investigators serve on the NORA Team for Occupational Cancer Research Methods. Some specific research activities are listed below:

In a study of cosmic ionizing radiation exposure among airline flight attendants, NCI and NIOSH are evaluating the use of various cytogenetic markers to improve exposure assessment. These biomarkers of exposure will be useful for research on breast cancer in this population. The project includes a methodologic component to develop procedures to estimate these exposures.

Researchers are conducting a retrospective mortality study and a nested case-control study of lung cancer in a cohort of non-metal miners to estimate the risk in relation to exposure to diesel exhaust. Excess mortality from other causes also will be evaluated. This study will advance the NORA priority areas of Exposure Assessment Methods and Risk Assessment Methods. An extensive effort to characterize current and historical exposures to the exhaust, and to develop estimates of personal exposures is an intrinsic part of the study. Another component of the study will relate biomarkers of exposure and effect to level of diesel exhaust exposure. We will examine whether exposed workers have detectable levels of nitro-PAH metabolites in their urine and nitro-PAH DNA adducts in a spectrum of tissues. This research will provide insight into the early biologic effects of diesel exhaust exposure and help clarify the biologic relevance of various components of diesel exhaust.

Methodologic procedures are being developed to fully utilize the availability of radiation badges among a cohort of x-ray technologists to assess cumulative level of exposure to radiation. The resulting exposure assessment method will be extremely useful in conducting cancer research in this population which, in turn, could have relevance to workers in occupations with similar cumulative levels of radiation exposure and to the general population.

Related to the NORA area, Surveillance Research Methods, NCI and NIOSH are continuing to coordinate efforts to code industry and occupational titles from death certificates from 25 U.S. States; creating a surveillance system that can be used to evaluate occupation and all causes of mortality, including cancer. The database has been used in numerous epidemiologic investigations.

NCI is working with NIOSH to improve the assessment of occupational and indirect bystander exposure to pesticides and other agricultural exposures in the Agricultural Health Study, a large prospective cohort study of approximately 90,000 people. The study includes licensed private pesticide applicators (mostly farmers), their spouses, and commercial applicators. The exposure assessment methods will have relevance for studies of pesticide exposure among occupational groups and among members of the general population.

In an ongoing collaborative study with NIOSH, NCI is evaluating the influence of genetic factors on bladder cancer risk among Chinese workers exposed to benzidine, an established bladder carcinogen.

In addition, NCI is currently supporting several other grants that responded to the NCI/NIOSH initiatives. These grants support advancement in methods of assessing environmental and/or

occupational exposures and the associated risks of developing cancer. They do so by developing and improving retrospective and surveillance methods to determine specific exposures to chemical and physical agents in various occupational and environmental settings.

NCI is also collaborating with NIOSH on an initiative called, "Endocrine Disrupters: Epidemiologic Approaches." This initiative solicits investigator-initiated studies on the role of endocrine disrupter chemicals (EDCs) in cancer development. EDCs are synthetic chemicals, used or manufactured in the workplace and released in the environment, that may cause adverse health effects by interfering with the function of the endocrine system. While it has been speculated that some endocrine-related diseases or conditions, such as breast and prostate cancers, are caused by EDC exposure, no linkage has been established between exposure to a specific environmental EDC and an adverse health effect in humans. NCI is expecting to support three to five new projects in FY 2002.

Item

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

Action taken or to be taken

The neurofibromatoses (NF) are genetic disorders that cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. Because NF may affect cognitive functions as well as hearing and sight, these disorders fall within the purview of a number of institutes within NIH, and attempts are being made to coordinate the research effort across NIH. For example, as part of a coordinated NIH effort to expand NF research, NCI participated in a 2-day workshop hosted by NINDS to assess the status of NF research and to identify future research opportunities. Besides NCI and NINDS, the meeting included a panel of 17 extramural basic scientists and clinicians, representatives from 4 NIH institutes (NICHD, NEI, NHLBI, and NIDCD), two other federal agencies with NF research programs (DoD and the Veterans Administration), the pharmaceutical industry, and two national NF patient advocacy groups. The meeting explored recent basic science or therapeutics research, and discussed proposals regarding research priorities and strategies in NF. Several priorities were agreed upon, including development of more refined animal models for NF1 and NF2; further analysis of the mechanisms of action of neurofibromin and merlin - the proteins whose functions are disrupted in NF1 and NF2 respectively; and the identification of modifier genes that affect the expression of neurofibromin and merlin. The results of this workshop were subsequently discussed with the broader NF research community at the annual meeting of the International Consortium for the Molecular and Cell Biology of NF1 and NF2. NIH institutes, including NCI, are working on developing several new NF- related initiatives to respond to the research needs and priorities identified through these meetings, and to stimulate interest in NF research from non-NF researchers. These initiatives will likely be focused on gene discovery research directly applicable to finding modifier genes for NF, and development of a registry for neurological disorders which would include a DNA collection

and facilitate natural history and genetic studies in NF. These initiatives will employ a variety of mechanisms - RFA, RFP, and investigator-initiated projects, as well as an additional workshop to facilitate NF clinical research.

NF is found in every racial and ethnic group throughout the world and affects both sexes equally. The disorders have been subdivided into neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). Other or variant types of NF may exist, but are not yet fully characterized. At least 85 percent are represented by Type I (von Recklinghausen or classic peripheral neurofibromatosis, with a prevalence of about 1:4,000 live births) and an additional ten percent by Type II (acoustic or central neurofibromatosis, with a prevalence of about 1:40,000 live births). Both NF1 and NF2 are autosomal dominant disorders with nearly full penetrance and both have a high rate of sporadic occurrence--about 30-50 percent. In both major forms of NF, severity of symptoms can vary greatly. Effects can be severely disabling, mildly disfiguring or can even go undetected.

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

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

One class of drugs that inhibits *ras* signaling is the farnesyl-protein transferase (FPTase) inhibitors, and NCI is supporting Phase I and Phase II trials of drugs in this class for the treatment of solid tumors and leukemias in both adults and children. NCI will soon begin accrual to a clinical trial studying the FPTase inhibitor R115777 for patients with NF1.

NCI will also participate in an ongoing multi-institutional study, called Protocol of the Natural History of Plexiform Neurofibromas in NF1, to assess the natural history of patients with NF1 and plexiform neurofibromas. The primary goals of the Natural History Protocol 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 IRB review. Clinical information about patients will be entered in a central database. Participation in this trial will allow NCI intramural scientists to expand their experience with NF1. In addition, patients in this study who develop disease progression will likely be eligible for participation in the Phase II trial of R115777.

NCI also supports clinical trials through the pediatric clinical trials cooperative groups that specifically include children with cancers associated with NF1. Of special concern are the brain tumors associated with NF1 and in particular the low-grade gliomas that develop in children with NF1. The NCI-supported Children's Oncology Group is conducting a clinical trial for children younger than 10 years of age with progressive low grade astrocytoma. The primary objective of the study is to compare event-free-survival (EFS) in children who are treated either with a regimen of carboplatin and vincristine (CV) or with a regimen of 6-thioguanine (6TG), procarbazine, CCNU, and vincristine (TPCV). Accrual is limited to children with disease that is progressive after surgery or whose risk of neurologic impairment with progression is high enough to require immediate treatment. Children with neurofibromatosis who have radiographic diagnosis of chiasmatic-hypothalamic tumor are eligible for the study after tumor progression is documented radiographically.

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

Item

Ovarian Cancer -- The Committee commends NCI for moving forward to fully fund two ovarian cancer SPOREs and partially fund two other ovarian cancer SPOREs in fiscal year 2000. The Committee encourages NCI to fully fund all SPOREs this fiscal year and requests that the Director of the Institute be prepared to give a progress report at the fiscal year 2002 appropriations hearing. (p.

59)

Action taken or to be taken

NCI is committed to improving the prevention, detection, and treatment of ovarian cancers. All four ovarian cancer Special Programs of Research Excellence (SPOREs) will be fully funded in FY 2001, and NCI expects these new ovarian cancer SPOREs – which support innovative, multidisciplinary research with the potential to have an immediate impact on cancer care and prevention – will be important hubs of progress against this disease. The SPORE program will be substantially expanded between FY 2001 to FY 2003 to add seven new cancer sites including a gynecological cancer solicitation in FY 2003. In addition, another ovarian SPORE solicitation will be issued in FY 2003.

Also, in early FY 2001, NCI established a Progress Review Group (PRG) to assist in setting long-term priorities for research on gynocological cancers, including ovarian cancer. Like other PRGs, this one is composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion by the end of FY 2001 and NCI will develop an implementation plan by mid FY 2002.

Item

Prostate Cancer --. . . . The Committee urges NCI to place an increased priority on research, through all available mechanisms, as appropriate, including clinical trials, that result in earlier, more reliable detection methods and more effective and less disfiguring treatment regimes. (p. 60)

Action taken or to be taken

The frequency and importance of prostate cancer as a serious health problem is well known and has been summarized by NCI in many places, so will not be repeated here.. The prostate cancer research agenda of the NCI is extensive and diverse. It includes studies to better understand the etiology (causation) and genetics of the disease, epidemiologic studies to correlate environmental, dietary, and genetic influences with risk, studies to determine the utility and optimal application of screening, studies to improve current treatments and develop new ones, and studies to assess patterns of care in the U.S.

NCI's prostate cancer research is guided by the results of the Prostate Cancer Progress Review Group (PRG) - a process in which experts and advocates in the field reviewed the NCI research portfolio and developed a comprehensive series of recommendations. The results of the PRG then served as the basis for developing a 5-Year Plan in late 1998 (Planning for Prostate Cancer Research: Five-Year Professional Judgment Estimates). In support of the PRG's recommendations and the 5-Year Plan, NCI substantially increased funding for prostate cancer research, from $86.9 million in FY 1998 to over $200 million in FY 2000. The report of the 5-Year Plan describes prostate cancer research

opportunities across NIH from 1999 through 2003. The scientific opportunities identified fell into four major areas:

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

Ongoing and future research initiatives have the potential to directly improve the length and quality of life of prostate cancer patients and survivors, as well as those at risk for the disease. Indeed, fully 70 percent of the research opportunities in the 5-Year Plan and discussed in this report are targeted at clinical or translational research that would have a direct impact on patients, survivors, and at-risk men.

Understanding the Biology and Etiology of Prostate Cancer

Current research suggests the presence of several prostate cancer susceptibility genes and of several potential environmental or dietary influences. However, searches for these are made difficult by the diversity and by the late onset of this disease, which greatly increase the complexity of dietary and lifestyle analyses and often precludes the examination of large families in which all members are currently alive.

The NCI SEER Program tracks prostate cancer incidence and diagnostic patterns in detail in 10 areas of the U.S. In collaboration with the National Center for Health Statistics, SEER tracks and publishes cancer mortality data for the entire country. The recently published Atlas of Cancer Mortality in the United States, 1950-94, characterized a distinct pattern of prostate cancer excesses among Caucasians in the Northwest, Rocky Mountain, and north-central areas of the U.S., and among African-Americans in the southeastern part of the U.S. After steady increases in the past several decades in prostate cancer mortality, a recent downturn was noted. These patterns are providing leads for further studies and for research in prostate cancer prevention.

The NIH-AARP Diet and Health Study is a prospective study of prostate cancer, with a focus on nutritional factors. The cohort is very large (over 540,000 men and women, over 320,000 men) and is characterized by a wide dietary intake range for several important dietary factors (fat, fiber, fruits and vegetables, red meat). Over 10,000 prostate cancers are anticipated during the first 5 years of follow-up; endpoints will be available in 2003. Pending the results of a pilot study, we expect to obtain buccal cell DNA from over 160,000 men, which will permit the examination of a number of gene-environment interactions in prostate carcinogenesis.

The International Consortium for Prostate Cancer Genetics (ICPCG) was formed in October 1996 to

address and overcome, through collaborative research the problems associated with prostate cancer susceptibility gene mapping and identification. This consortium consists of over 20 institutions in seven different countries in North America, Europe and Australia, all with ongoing research programs in this area. The size and diversity of this group, including families from diverse ethnic and racial groups, makes it ideally suited to address questions pertinent to the molecular genetics and genetic epidemiology of prostate cancer, including the understanding of different genetic etiologies (genetic heterogeneity), gene-gene interactions, and other cancers with increased occurrence in prostate-cancer families. A primary goal of the ICPCG is to rapidly and efficiently test promising hypotheses that have been generated by individual research groups. Members of the ICPCG have already carried out a collaborative analysis of data linkage for identified markers for new susceptibility genes in 772 families, and have conducted a genome-wide scan in most of the participating families to identify new susceptibility loci.

Cancer Genetics Network (CGN): Established in 1998, the CGN is a national Network of centers specializing in the study of inherited predisposition to cancer. Consisting of 8 centers and an Informatics and Information Technology Group, CGN supports collaborative studies on the genetic basis of cancer susceptibility, mechanisms to integrate this new knowledge into medical practice, and means of addressing the associated psychosocial, ethical, legal, and health issues.

Gene discovery research is being developed in consultation with other prostate cancer gene discovery activities, such as the ICPCG and the Specialized Programs of Research Excellence (SPORE) for prostate cancer. (The prostate cancer SPORE was developed to promote interdisciplinary research and to speed the bidirectional exchange between basic and clinical science in order to move basic research findings from the laboratory to applied settings involving prostate cancer patients and populations.)

The Cancer Genome Anatomy Project (CGAP) is a project to build an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. The tumor type with the highest representation in the early stages of the CGAP effort is prostate cancer. NCI has facilitated investigator collaborations of interdisciplinary studies following the recent discovery of a susceptibility gene for prostate cancer. Leads from this effort may also help to clarify genetic and gene-environment interactions responsible for African-American-Caucasian differences in risk.

Other epidemiologic studies underway include: a large cohort study of agricultural workers in the U.S. upper Midwest and the Southeast to examine suspicions that farming practices are related to the elevated prostate cancer risks in this population; a collaborative case-control study with the University of South Carolina to address risk factors for prostate cancer in high-risk areas of the U.S. identified by the new NCI cancer maps; a collaboration with Norwegian and CDC investigators regarding environmental exposures to DDT and PCB congeners; a U.S. population-based case-control study investigating the increased risk of prostate cancer among men with a history of gonorrhea or syphilis; a systematic pathology review of approximately 1,000 cases of incident prostate cancer in Israeli Ashkenazi men diagnosed from 1994-1995 to determine the age-specific carrier rate of BRCA1 and

BRCA2 mutations in this population and to determine if there are distinguishing features of BRCA-associated prostate cancer; a study of the effects of in utero exposure to diethylstilbesterol (DES) on prostate cancer risk are being evaluated in the sons of DES-exposed women; a study of the associations of high levels of insulin-like growth factor (IGF-1) and low levels of it's major serum binding protein (IGFBP-3) with prostate cancer risk in Washington Co., MD and in Hawaii; and a study of the types of fat associated with prostate cancer risk among African-Americans, Caucasians, and Asians.

NCI is organizing a major meeting, "Emerging Opportunities in Prostate Cancer Epidemiology", which will address gene discovery and gene-environment interactions research directions and strategic approaches, with a special emphasis on multiethnic variation, i.e., health disparities.

After completion of enrollment to the first national prostate cancer prevention trial (PCPT-1), a larger study of 32,000 men is being launched this year. The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) will serve as a major test of dietary supplementation to reduce the risk of prostate cancer development in moderate-to-high risk individuals.

Screening

Public awareness of prostate cancer and participation in both early detection and screening programs have increased markedly in the U.S. over the last decade. Encouragingly, a national decrease in mortality from prostate cancer has been observed since 1992. Although it is easily assumed that this represents a benefit of screening programs, careful analysis of the geographic and annual data by extramural and NCI epidemiologists suggests that that explanation, at most, accounts for only a small proportion of the mortality trend. A substantial proportion of the mortality improvement may be related to a vastly increased and much earlier utilization of therapies such as radiation and hormones for patients with only biochemical (PSA) evidence of recurrent disease. There may also be substantial effects from life style or dietary trends of the past 2-3 decades, or other factors. Research into these issues is a major project of NCI.

It is very difficult to dissect the various influences on mortality in population studies. For this purpose, a randomized intervention trial is the most direct and definitive approach. NCI's PLCO, launched in 1993, is a large U.S. multi-center randomized controlled trial assessing the efficacy of prostate cancer screening versus a non-screening strategy. If the mortality effects are as large as some suppose, and if they are apparent within only a few years from initiating screening programs, then the PLCO trial should be able to detect a benefit within only a few more years. In addition, within the PLCO trial, NCI Intramural investigators are examining genetic and environmental risk factors that may shed light on issues of susceptibility and causation.

The National Health Interview Survey (NHIS) is a large, annual population-based health survey sponsored by CDC and NCI. The 2000 NHIS will provide information on prostate cancer screening habits by collecting information from approximately 40,000 households with an over-sample of African-American and Hispanic populations. NCI also initiated an international collaboration among

researchers in Europe and North America conducting prostate cancer screening randomized trials known as the International Prostate Screening Trial Evaluation Group (IPSTEG). The purpose of this collaboration is to develop and implement an evaluation plan for the joint analysis of randomized trial data on prostate cancer screening using prostate specific antigen (PSA). A combined analysis offers increased statistical power and a larger, more informative database over an individual study. The total sample is anticipated to be in excess of 300,000 men, with a follow-up period of at least 10 years.

On the public education side of screening, several of the NCI's Special Populations Networks are working with the NCI Cancer Information Service and are involved in disseminating information on prostate cancer issues including the potential benefits and risks of screening. Also, information specialists from the Cancer Information Service provide more than 60,000 people annually with information about prostate cancer, research on the disease, screening and treatment options, and information about coping with physical and psychological side effects of the disease and its treatment. The NCI web site provides information about clinical trials as well as information about treatment options for every stage of prostate cancer.

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

Segregating Aggressive from Indolent Prostate Cancers

Satisfactory answers to many current dilemmas in management of prostate cancer patients - for example, the role of routine screening, or initial management by prostatectomy versus radiation versus watchful waiting - may only be found when we know enough about individual tumors to predict their individual behavior and assess their vulnerabilities. The tools we currently have for determining which prostate cancers are most likely to recur are crude and imperfect. We can estimate this very approximately by using the tumor appearance under a microscope, the stage, and the PSA level; but there is so much overlap that the decision making for many patients is still terribly difficult. If we had better ways to classify whether an individual patient's tumor is one with a high malignant potential or one of the larger number that poses considerably less risk, then we could much more easily test early detection and screening technologies, and provide the confidence that could spare many men the long term side effects of prostate surgery or radiation.

A goal for the next several years is to develop what has been called "molecular profiling" or "molecular signatures" – the identification of patterns of gene and protein expression abnormalities that will someday enhance a clinician's ability to predict the behavior of a particular cancer. Two of NCI's largest projects, both of them identified as Extraordinary Opportunities in the NCI's Bypass Budgets, provide the infrastructure for grappling with this need. The CGAP has thus far discovered more than 150 genes that appear to be prostate-specific, and over 400 genes that appear to be expressed

differently between normal prostate tissue and prostate cancer. This information, and subsequent discoveries of CGAP, will provide the raw material for the next initiative, the NCI Director's Challenge for Molecular Diagnostics. The goal of the Director's Challenge is to develop a tumor classification system that is firmly based on the cell biology of cancers, rather than on microscopic appearance.

Prostate cancer is a particularly important area of application for this initiative, because its behavior is so variable from patient to patient. This variability underlies many of the unresolved or controversial clinical issues and confounds our ability to make definitive recommendations that apply broadly to most patients. Thus, it would be difficult to overestimate the potential benefit to patients with prostate cancer of progress in this direction of molecular signatures and molecular classifications.

Clinical Trials

NCI sponsors a very large number of prostate cancer clinical trials by grants to individual investigators in hospitals and academic institutions, grants to cancer centers and large multi-center research consortia, by collaboration with pharmaceutical and biotechnology firms, and within its intramural programs. These trials range from small-scale early testing of novel agents, or new combinations, to very large-scale and definitive randomized trials that can establish the value of a new intervention, and include studies of all types, including treatment, prevention, screening and early detection, supportive care, symptom management, and others.

The recent requirement that HCFA cover the patient care costs for Medicare beneficiaries enrolled in clinical trials sets a national precedent and is a win-win for both researchers and patients. It expands patients' opportunities to enroll in leading-edge clinical research, promotes the development of clinical trials that address questions specific to the elderly, and allows important clinical research questions in prostate cancer to be addressed.

Last year, NCI funded (in total or in part) 246 clinical trials in prostate cancer, including 80 Phase III studies and 37 Phase II treatment studies. Many of the larger studies were intended to test and optimize new hormonal and chemotherapeutic approaches for the most common clinical presentations of the disease, including:

- **$** adjuvant therapy or neo-adjuvant therapy (intended to prevent recurrence) when added to primary surgical or radiation treatment
- **$** treatment in the setting of rising PSA levels after definitive local therapy
- **$** treatment after hormone therapy is no longer effective
- **$** advanced disease, particularly directed at bony metastases

As part of ongoing initiatives to expand access to clinical trials for larger numbers of cancer patients and to make the state-of-the-art treatment they provide a viable therapeutic option for patients in most clinical settings, NCI has broadened eligibility criteria for many of its clinical trials. Clinical trials have also been developed for stages of disease that were not often studied previously. Clinical trials for prostate cancer patients with rising PSA as the only indicator of disease recurrence are an example of

this approach. In order to provide earlier access to novel agents, NCI has developed ways to enroll patients with more advanced disease on clinical trials, whether or not they have already received conventional hormonal therapy. These approaches offer greater participation in therapeutic decision-making and autonomy for well informed patients who desire more novel experimental approaches despite potentially greater risks.

NCI's extensive early therapeutics development program for novel chemotherapy and immunologic agents sponsors many small exploratory trials in prostate cancer and other tumor types. Among the promising new approaches currently under study are inhibitors of angiogenesis and metastasis, the processes by which cancers induce new blood-vessel formation, invade these blood vessels, and spread throughout the body; growth factors and their receptors, which mediate growth signals to cancer cells; tissue-specific genes expressed selectively in prostate or prostate cancer cells, thus allowing for the targeting of tumor-killing modalities to these cells; monoclonal antibodies; vaccines; hormones; and agents targeting bone as the major site of spread for prostate cancers, as well as combinations of these agents with others or with radiation therapy. These agents and approaches could not all be catalogued here in any degree of detail and in any case the results are not mature.

Some other important developments of very general interest include:

- NCI's Prostate Cancer Prevention Trial (PCPT-1) is the first major trial of chemoprevention in prostate cancer. 18,000 healthy men over the age of 55 were enrolled to determine if the drug finasteride could prevent development of prostate cancer. A second, larger study of 32,000 men will be launched this year. The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) will serve as a major test of dietary supplementation to reduce the risk of prostate cancer development in moderate-to-high risk individuals.

- Using data collected within the Prostate Cancer Outcomes Study (PCOS), investigators have found that patients with clinically localized cancer who undergo radical prostatectomy have less aggressive cancers compared with men who receive external beam radiotherapy. Almost 2 years after treatment, men receiving radical prostatectomy were more likely than those receiving radiotherapy to be incontinent (10 percent versus 4 percent) and to have higher rates of impotence (80 percent vs. 62 percent), although large, statistically significant declines in sexual function were observed in both treatment groups. Men undergoing radiotherapy reported greater declines in bowel function. These estimates of long-term treatment complications are much higher than estimates from previous studies conducted in major academic medical centers. Other PCOS-based studies have reported on health outcomes following radical prostatectomy, the value of diagnostic imaging studies, and the probability of pathologically advanced disease among men undergoing radical prostatectomy for suspected early stage disease. Forthcoming studies using PCOS data will examine treatment complications following radiation therapy and hormonal therapies, and the contribution of sociodemographic and clinical factors to population patterns of treatments used for early stage prostate cancer.

- Data such as those collected by PCOS re-emphasize the fundamentally critical role still required of carefully designed prospective randomized trials in dissecting the effects of treatments from the effects of patient selection (including self-selection) for particular treatments. The breakthrough Prostate Cancer Intervention Versus Observation Trial (PIVOT) that has been sponsored by Department of Veteran's Affairs with assistance of NCI should complete accrual by December 2001. This randomized Phase III trial, which many had feared could not be completed, will compare the long term outcomes of "watchful waiting" with those of initial surgical removal of the prostate. This trial is intended to determine whether conservative treatment of localized disease may be an acceptable alternative to surgery, at least for some patients.

- A longstanding highly controversial question is whether earlier use of hormonal therapy (androgen deprivation) can prolong survival for prostate cancer patients who have not been cured by initial prostatectomy or radiation. An NCI Intergroup trial that addressed this question in one very high risk setting demonstrated dramatic differences that, together with other evidence, support the assumption that early androgen deprivation may be of benefit in prolonging survival, and not just in shifting the timing of recognition of advanced disease.

- In recent years, to accommodate an expansion of the clinical trials effort and meet the challenge of an explosion of new knowledge and promising new classes of agents, NCI has received the advice of panels of external scientists, researchers, cancer survivors, ethicists, and representatives of professional organizations regarding the framework of NCI's large randomized treatment trials (in all cancers). This process led to recommendations for substantial restructuring consisting of a series of new initiatives and pilot projects. Together, when fully operational, they are intended to improve the quality and speed of clinical trials, improve access to trials for patients and doctors, and foster innovative clinical research that hastens the transition from laboratory to patients. Details of the Clinical Trials Restructuring effort can be found at http://plan2002.cancer.gov/infenhancing.htm and therefore will not be detailed here. However, because of its public health consequences, prostate cancer was selected as one of the two tumor types in which all of these new initiatives would be tested.

- It should be noted that all of these new initiatives are inherently open, competitive ones – they do not specify that the interventions be drugs; they could be dietary supplements, surgical procedures, new radiation techniques, or gene therapies. Also, they may be intended for either treatment of established prostate cancers, or for prevention; they may arise within the "conventional" medical research community, or from the alternative medicine community, from academia, or from industry.

- New mechanisms for strengthening of the translational interface between laboratory and clinic is in many ways the most delicate and vulnerable part of the entire clinical trials enterprise. Several new methods were developed to accomplish this goal in different settings: a Clinical Oncology Special Emphasis Panel established by NIH's Center for Scientific Review; funding for correlative science studies that accompany clinical trials via a Program Announcement inviting submission of R01 and R21 grant applications; developmental funds in the cooperative groups to support the generation of pilot data upon which subsequent R01 and R21 applications may be based.

There are also other new and ongoing projects that address issues closely related to clinical trials and patient outcomes. For example:

- The Cancer Care Outcomes Research and Surveillance Consortium (CANCOR) is a new multi-center project consisting of several research center/cancer registry partnerships coordinated by a single data coordination center. CANCOR is the first major step by NCI to develop a system for obtaining details about cancer care beyond the initial surgical and radiation treatment that is already routinely collected in the SEER Registry. This will complement the SEER Program and other population-based cancer registries and build the information base needed for measuring and improving the quality of cancer care in the U.S. A substantial goal of CANCOR is to examine disparities in the receipt of state-of-the-science cancer care and factors that contribute to disparities in outcomes (such as health-related quality of life) and identify ways to lessen those disparities.

- The NCI-sponsored Cancer Information Service provides more than 60,000 people annually with information about prostate cancer, research on the disease, screening and treatment options, and information on coping with the physical and psychological side effects of cancer and its treatment. The NCI web site provides information about prostate cancer clinical trials as well as information about treatment options for every stage of the disease. NCI's basic print product about the disease, What You Need to Know About Prostate Cancer, is now available on the web. A new NCI publication, Understanding Prostate Changes: A Health Guide for All Men, will soon be available on the web. It covers all aspects of prostate cancer in more depth than the basic booklet, but also describes non-cancerous prostate conditions. Another product in development, called Prostate Cancer Treatment: Know Your Options, will be published in print format soon and will also be available on the NCI web site.

Accelerating Drug Development

Although there are more new types of agents now in development than ever before, there are many necessary steps on the path between the laboratory bench and clinical use in patients. Large pharmaceutical firms may have all the necessary resources available to them, and the NCI itself has been able to carry out all the steps for agents in its own development portfolio. However, many independent investigators in universities or in small or medium size biotechnology companies have faced major delays in completing the work needed before a new agent can start human testing, or in funding the first human trials to find out if an agent appears promising. NCI has thought carefully about the kinds of barriers that exist in these situations, and developed a package of new programs to fill in the gaps and accelerate the drug development process.

- The Rapid Access to Intervention Development (RAID) and Rapid Access to Prevention Intervention Development (RAIPID) programs are intended to expedite new agent development by moving novel molecules toward clinical trials. Often academic investigators do not have the resources or cannot afford to complete all safety testing or carry out formulation of an agent in such a way that it can be given to patients. NCI has created a process that enables investigators to

advance novel molecules to clinical trials when they have not yet found a pharmaceutical or biotechnology industry partner with the necessary resources. This is done by giving academic investigators access, on a competitive basis, to NCI's preclinical drug development resources and expertise. Investigators who have molecules that hold promise for cancer treatment are invited to submit applications twice a year. Those selected for support are assisted with necessary development steps to enable Investigational New Drug Application (IND) filing with the FDA and to begin initiation of proof-of-principle clinical trials. The investigators are then free to develop industry collaborations in whatever way that suits them.

- The "Quick Trials" program is the next step to actually carry out the preliminary patient clinical trials to find out how best to apply the new intervention and whether it actually does appear to do something useful in patients. These studies are time-consuming and personnel intensive, and may require sophisticated laboratory or imaging tests. It is increasingly difficult in today's medical care system to do such trials without grant funding, and it's difficult to get a conventional grant with little preliminary data. There also can be frustrating and unsatisfactory delays. For this reason, the Prostate Cancer Quick Trials program was developed by NCI in 1999 to provide a rapid, streamlined funding mechanism for moving novel new ideas for therapeutic interventions into Phase I and II clinical trials for prostate cancer. This program has been set up in recognition of the urgent need for new types of interventions that are effective at different stages of prostate cancer, as well as the growing number of therapeutic ideas that are ready to be tested in patients. After piloting this new approach in prostate cancer, it was expanded to all cancers in 2000.

Minority Issues

Population differences in incidence or mortality of a particular cancer may arise because of genetic factors, environmental exposures or dietary differences, as a consequence of socioeconomic phenomena such as education, access to care, and behavior; or by some combination of these. In order to determine which factors are important, it is necessary to carry out all of the following types of scientific studies: surveillance studies in which information is collected on large populations, interventional studies in which some factor is modified, and biologic studies that examine the cancers and the patients themselves.

The Prostate Cancer Outcomes Study (PCOS) was initiated in 1994. This large, community-based study provides information about reasons for variations in prostate cancer diagnostic and treatment practice patterns, and describes health-related quality of life (HRQL) following treatments for clinically localized and metastatic prostate cancer in a representative patient population. The size and design of the study permits evaluations of variations in diagnostic and treatment practices, and HRQL, according to geographic region, racial/ethnic sub-groups, income, education, and health insurance status. In a recent study, PCOS investigators found African-American and Hispanic men had an increased relative risk for presenting with advanced stage cancer. Traditional socioeconomic, clinical, and pathologic factors accounted for the increased relative risk for Hispanics but not for African-Americans. African-Americans had more aggressive tumors, suggesting that tumor biology and unmeasured socioeconomic factors may account for the disparity in cancer stage at diagnosis.

SEER Program data also have shown differing patterns of care among African-American and Caucasian men with prostate cancer. African-Americans with local/regional prostate cancer are far less likely to be treated with radical prostatectomy or external beam radiation. Studies are now geared toward determining the reasons for these disparities in care. Encouragingly, however, NCI and DOD staff have shown that equal treatment yields equal outcome within disease stages. This finding suggests that NCI efforts to improve prevention, diagnosis, and treatment of this disease have the potential to benefit all patients equally.

Genetics and Gene-Environment Interactions: The NCI funds a number of studies comparing populations to assess genetic variation and gene environment interactions that may lead to the varied incidence of prostate cancer. These studies include large scale epidemiologic studies and are often linked to basic science laboratory projects. Below is a summation of several ongoing NCI sponsored research projects and their findings to date:

- A case control cohort study of a multi-ethnic group of 202,136 individuals in the Western U.S. to determine the genetic risk of prostate and several other cancers. This cohort is of sufficient size and heterogeneity to study the relationship between environmental risk factors and genes that may be important alone or as sources of potential interaction in determining the risk of sporadic cancers of the colorectal, prostate, and breast. This project has a substantial number of African-Americans, Hispanics, Japanese-Americans and Caucasians. The study investigates polymorphisms in candidate genes that might alter metabolism of endogenous or exogenous exposures, and their interactions with dietary variables (e.g., saturated fat and fiber intake) and other exogenous exposures (e.g., hormone replacement therapy) that affect the risk of these three cancers. This work is being done by researchers at the University of Hawaii and the University of Southern California.

- Several NCI studies are assessing the association among 5 alpha-reductase genotype, race, obesity, diet, physical activity, and prostate cancer risk. One such study is a collaboration with the National Heart Lung and Blood Institute to increase efficiency. This study evaluates lifestyle and genetic determinants of serum steroid hormone and binding protein levels in 631 African-American and 873 Caucasian male participants of the Coronary Artery Risk Development in (Young) Adults (CARDIA). Investigators will utilize previously collected and stored serum and DNA samples. Results of this study will provide the first longitudinal analyses of steroid hormone changes and their correlation in a bi-racial population.

- The Shanghai Prostate Cancer Study is a population-based case-control study of prostate cancer in China, where the reported incidence for clinical prostate cancer is the world's lowest, but rising rapidly. To date, the study has provided etiologic leads to help clarify the reasons for the substantial racial difference in prostate cancer risk.

- One, case-control study compares prostate cancer risk for African-American (449 cases, 543 controls) and Caucasian men (483 cases, 658 controls). So far, the study has found that risk for

the disease is increased among the brothers and fathers of men with a history of prostate cancer and for heavy users of alcohol. A study of dietary patterns linked greater consumption of fat from animal sources to increased risk for prostate cancer for both African-Americans and Caucasians. Use of tobacco did not appear to be related to prostate cancer risk.

- A population-based-case-control study of occupation and prostate cancer in Detroit examines the effects of occupational exposures on the subsequent risk of prostate cancer. Thus far this and other studies have linked work in cadmium-contaminated environments with increase risk of prostate cancer.

- A study of farmers and their families (The Agricultural Health Study) is a prospective cohort study of about 90,000 Americans, in collaboration with NIEHS, NIOSH, and EPA. The study includes licensed private pesticide applicators, their spouses, and commercial pesticide applicators. Pesticides, sunlight, viruses, mycotoxins, well water contaminants, and a variety of other occupational exposures are suspected to play a role in the observed excess risk of prostate and other cancers. Investigators will also examine disease risks among spouses and children of farmers.

- An sero-epidemiologic prospective study hopes to identify biochemical markers related to common cancers occurring among 11,132 American Japanese subjects examined in Hawaii. Investigators will use the subjects' frozen stored serum obtained years prior to the diagnosis of cancer to determine whether low serum selenium or isoflavonoid levels increases the risk of prostate cancer.

- Research is on-going at the NCI on inter-individual variability in genes that regulate androgen activity and their effect on individual susceptibility to prostate cancer. Androgenic hormones are essential to prostate function and are believed to play a key role in prostate carcinogenesis. NCI investigators confirmed that healthy Chinese men tend to have long series of CAG nucleotide repeats in the androgen receptor gene. This trait is associated with reduced androgenic activity and is consistent with the observation that Chinese men have a low risk for prostate cancer. The investigators also showed that Chinese prostate cancer cases had shorter CAG repeats in the androgen receptor gene compared to healthy control subjects, indicating that CAG repeat length can potentially serve as a useful marker to identify individuals at high risk for clinically significant prostate cancer.

- NCI is currently funding four Specialized Programs of Research Excellence (SPOREs) grants conducting prostate cancer research. These were recently augmented to increase their emphasis on cancer etiology, especially etiology in African American populations and comparisons between African and Asian American men, and to enhance training opportunities for minority pre-doctoral and post-doctoral individuals. An underlying theme of research training in prostatic neoplastic diseases in African Americans will be gene-lifestyle interactions and patterns of medical care that impact prognosis, quality of life and mortality. SPORE supplements will also support diagnosis and evaluation of biological aggressiveness and treatment options in African American men, and a high-density tissue microarray of prostate cancer tumors that will facilitate examining the influence of race along with molecular, pathological, and clinical factors.

- Studies involving culturally diverse populations of prostate cancer survivors and their partners will assess the long-term impact of the treatment regimens used for prostate cancer. Investigators will survey about 2100 patients and 1650 spouses, using a cross-sequential design to assess QOL, depression, and treatment satisfaction at 5, 8, and 11 years post treatment. Of interest is how outcomes vary according to ethnicity (Chinese, Filipino, Hawaiian, Japanese, and Caucasian) and primary prostate cancer therapy (surgery, radiation, other).

- Information Dissemination: NCI sponsored assessments of the needs of minority lower socio-economic cancer patients demonstrate the need for cancer related information and improvement of skills to manage pain. Several studies are currently aimed at developing multi-media education and training materials that are linguistically and culturally appropriate for Hispanic and African American populations. One study, entitled Information Needs of African American Cancer Patients, consisting of random sample of 250 African American and 250 Caucasian prostate cancer patients and their families, explores the interconnection of such factors as patient information seeking, patient-provider communication, participation in treatment decision making, and emotional adjustment.

- Several of the NCI's Special Populations Networks are working with the Cancer Information Service and involved in information dissemination on prostate cancer issues including the potential risks and benefits of screening. The National Black Leadership Initiative on Cancer, for example, has linked with the 100 Black Men of America and other African-American fraternal organizations to provide information and sources from which one can obtain more detailed information when needed.

- NCI funded (in total or in part) 246 clinical trials in prostate cancer, including 80 Phase III studies and 37 Phase II studies. NCI clinical studies in prostate cancer have significant African-American participation. One study shows that 14.7 percent of men enrolled onto NCI sponsored prostate cancer treatment trials are African American while 10.3 percent of Americans diagnosed with prostate cancer are African American.

- All NCI clinical trials, whether large or small, routinely examine outcome data to determine if there appears to be a difference in response to treatment with regard to race or ethnicity. Of course, only large trials can determine this with a good degree of statistical certainty. Thus far, there is very little evidence that suggest that there are differential responses to therapy in different racial groups. However, even in the initial trials of new agents (which are necessarily small trials), NCI scientists look for trends that suggest differences that should be looked for when larger studies are designed.

- NCI, along with the American Cancer Society and the Centers for Disease Control and Prevention sponsored a Leadership Conference on Prostate Cancer in the African-American Community in November of 1997. Developed in cooperation with the 100 Black Men of America, the Intercultural Cancer Council, the National Black Leadership on Cancer, and the National Prostate

Cancer Coalition, the conference represented a significant step toward developing a strategy for the full participation of African Americans in prostate cancer research and control.

Quality of Life

Decisions about treatments are not easy to make. At present, it is difficult to predict whether a tumor will grow slowly with no health consequences to the patient or grow quickly and become life-threatening. Also, except for the PIVOT study previously discussed, there are few randomized trials that compare the relative benefits of treating early stage patients with radiation therapy, radical prostatectomy (surgical removal of the entire prostate gland along with nearby tissues), or watchful waiting (following the patient closely and postponing aggressive therapy unless symptoms of the disease progress). In spite of these uncertainties, it is known that certain treatments -- radiation therapy, radical prostatectomy, or hormonal therapies -- can have detrimental effects on urinary, bowel, and sexual functions. To date, there have been no accurate estimates of the changes in functional status among men treated in everyday community settings.

The PCOS, discussed above in section four and Minority Issues, includes among other goals an evaluation of the impact of treatments for primary prostate cancer on long-term complications and the quality of life of patients. PCOS is the first systematic evaluation of health-related quality-of-life issues for prostate cancer patients conducted on a multi-regional scale, and includes approximately 3,500 men diagnosed with the disease. By collecting patient survey data on the health outcomes of various treatments for prostate cancer, the PCOS will help patients, their families, and physicians make more informed choices about treatment alternatives.

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

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

Expanding Research

NCI's commitment to expanding all aspects of prostate cancer research can be appreciated by the

increased funding over the last 3 years, from $86.9 million to over $200 million in FY 2000, and by the strategic planning in the form of the Prostate Cancer Progress Review Group (PRG) and the coordinated, trans-NIH prostate cancer 5-Year Plan presented to Congress.

In support of these goals, and in follow-up to the PRG, NCI has:

- Identified more than 20 initiatives through which high priority areas can be addressed and established a special section of the NCI Web site serves to bring these to the attention of researchers and the public.

- Further emphasized the importance of accelerating the pace of progress against prostate cancer by pledging and publicizing that prostate cancer grant applications will have priority for so-called exception funding. That is, every effort will be made to fund worthy applications in the identified high-priority research areas even when peer-review assigned priority scores are not quite high enough to fit within conventional grant award paylines.

- Met with the representatives of the prostate cancer research community, the PRG, and the leadership of professional societies, such as the American Urological Association, to communicate these initiatives and to enlist their support.

- Established extensive outreach programs and advertising to alert the larger research community to these opportunities to energize their participation in this prostate cancer research program. The promotion includes information on the web site, the placement of advertisements in major scientific journals, distribution of packets of information to the nation's cancer centers, and the distribution of information through direct mail to cancer investigators. Since the promotion began in 2000, the web page listing prostate cancer grant opportunities has had thousands of hits from those seeking information about the grant opportunities.

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

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

It is anticipated that these will be productive areas of future research, as will others, as yet unrecognized. Hopefully, the next several years will yield many advances that will further accelerate progress towards

conquest of this devastating disease and better lives for an ever larger group of prostate cancer survivors.

Item

Rural Poor in Health Disparities Research -- While studies have shown that certain diseases effect minority groups, economic status may also have an impact on health outcomes. For example, the rural poor have a high incidence of cancer. The Committee urges NCI to include the rural poor population in its efforts to eliminate health disparities. (p. 60)

Action taken or to be taken

With respect to cancer surveillance, it is important to describe accurately the differential cancer burden in low income, rural populations. In FY 2001, the SEER Program added four new cancer registries through a competitive selection process. The choice of additional registries was finalized on a balance of consideration of the coverage of populations of interest and the readiness of the registries in place, with particular emphasis on populations for which limited data currently exist, such as rural low-income whites, American Indian populations, rural African-Americans, and other Hispanic groups. During the next 3 years, NCI staff will work closely with the CDC staff who manage the National Program of Cancer Registries (NPCR) to coordinate parallel implementation of the SEER geographic expansion with enhancements for NPCR states to increase the number of population-based registries with high quality data and coverage of rural poor populations.

The NCI recently posted on its website for comments, a draft of its Strategic Plan to Reduce Health Disparities, that is part of a major national commitment to identify and address the underlying causes of disease and disability in racial, ethnic, and socio-economic communities throughout the country. Because these communities carry an unequal burden of cancer-related health disparities, NCI recognizes the need to greatly enhance our research, education, and training programs that target these pockets of need. From cancer prevention to clinical trials recruitment to cancer survivorship, the NCI Strategic Plan will help us understand the causes behind health disparities in cancer and to develop the most effective and culturally sensitive ways to work with underserved communities to eliminate these disparities. NCI also established the Center to Reduce Cancer Health Disparities to oversee the implementation of NCI strategic plan to reduce cancer-related health disparities and find ways to turn research discoveries into the delivery of services to reduce these disparities.

National mortality data by age, sex, race, and county of residence are available annually in electronic form for the U.S. from 1968 through 1998. The quality of socioeconomic (SES) data (e.g., educational attainment, occupation, income, poverty, unemployment, home ownership, wealth or housing condition, and industry of the decedent) on the death certificate is poor, incomplete, and not consistently available prior to 1985. The population denominator data needed to calculate SES-specific rates are generally not available except for the decennial census years. Analytic approaches that link mortality data with census-derived socioeconomic and demographic variables at an aggregate geographic level such as county are extremely useful in ecological surveillance of cancer among various

area-based socioeconomic groups (e.g. Rural poor). Single measures of areal socioeconomic status or a composite SES or socioeconomic deprivation index that statistically combines some or all of these indicators can be used to stratify all U.S. counties into a few county groups or population strata (e.g., quintiles) whose relative socioeconomic standing remain relatively stable and robust across time. It can be shown empirically that the areal socioeconomic classification (measured in quintiles) remains more or less unchanged over the 1970-1990 period whether one chooses the 1990, 1980, or 1970 Census to obtain county-level socioeconomic variables. It is possible to calculate annual sex-, race-, SES- and site-specific cancer mortality rates across time. This approach has been used to analyze changing socioeconomic patterns in lung and prostate cancer mortality among men. A similar strategy examined spatial and temporal trends in socioeconomic differentials in cervical and breast cancer mortality.

Examination of SES differences in cancer incidence, disease stage, and survival, is being investigated by linking census-based SES data to the SEER registry data at the tract-level, a fairly homogenous geographic unit that is common to both the Census and SEER databases. Regression models are fit to evaluate the effects of areal SES on site-specific cancer incidence after adjusting for age and ethnicity. Socioeconomic differences in survival and stage at diagnosis can be examined in a multivariate framework in which each cancer record is assigned a SES index score or category based on the tract-level census data to look at ethnic and SES differences in cancer survival adjusted for stage, age, birthplace, marital status, and place of residence (rural vs. Suburban vs. Urban).

With respect to intervention research, education and training, the Appalachia Leadership Initiative on Cancer (ALIC) was instrumental in launching collaborative efforts to raise cancer awareness, improve access to care, and reduce the cancer burden in Appalachian populations. The overall goal of this research initiative was to mobilize Appalachian community leaders to develop coalitions to promote cancer prevention and control and to evaluate the impact of research interventions. Among the ALIC's priorities were the promotion of smoking cessation, diet modification, and screening.

NCI recently launched the Special Populations Networks for Cancer Awareness Research and Training aimed at improving cancer prevention and control in minority and underserved communities. The Appalachia Cancer Network (ACN) builds upon and expands the scope of the ALIC. The Markey Cancer Center at the University of Kentucky, in collaboration with its key consortium affiliates (Pennsylvania State University and West Virginia University), regional partners and community-based cancer control coalitions, established the ACN. The ACN will address critical cancer control issues that impact rural, medically-underserved population of Appalachia in the states of West Virginia, Kentucky, Tennessee, Virginia, Ohio, Pennsylvania, Maryland, and New York. The ACN will expand cancer control awareness within rural, underserved, and minority populations of Appalachia, and through research and cancer control activities will address the key barriers to utilization of cancer control services and optimal cancer care within the Appalachian region. The long-term goals of the ACN program are to reduce cancer incidence and mortality and prevent future increases; reduce barriers to accessing cancer control services and programs (national, state, and local) and increase utilization of such services; increase cancer survival; and stimulate greater coordination and participation among regional, state, and community cancer control networks throughout Appalachia.

NCI's rural research portfolio in FY 1999 encompassed 19 research projects totaling $8.1 million in funding. Prevention intervention projects included reducing pesticide exposure and increasing safe handling among Vermont farm families, promoting increased fruit and vegetable consumption among rural children in Minnesota, research to reduce tobacco use and promote low fat/high fiber foods among sixth graders in rural Virginia and New York schools, promoting cessation of smokeless tobacco use among baseball athletes attending rural California high schools, and exploring dietary habits and reinforcing health nutrition among Native Americans in four California rural Indian sites compared with four urban settings. Early detection research included a study to promote early detection of breast cancer in low income rural women, 50 years of age and older, in Robeson County, North Carolina. Recently completed studies included increasing mammography use among older, minority and rural women, and cancer pain management in community-based rural settings.

Information dissemination to medical professionals and residents of rural America is vital. The gap between people who have access to the latest information technologies and those who do not is widening. Those on the "have not" side of the Digital Divide typically experience the negative effects of health disparities. Income is now the greatest determinant of lack of access. The NCI is committed to expand its investment in cancer communications in order to increase demand for, access to, and use of online and other interactive cancer communications by diverse populations. The NCI's Cancer Information Service is in an ideal position to reduce the impact of the Digital Divide and has been challenged to increase usage of online cancer information services.

The planned Cancer Communications Centers of Excellence are an integral part of our plan to provide the essential infrastructure needed to facilitate rapid advances in knowledge about cancer communications, develop evidence-based strategies and tools for cancer communication, train tomorrow's health communication scientists, and promote collaboration with the Cancer Information Service and partnerships with advocacy groups, industry and commercial endeavors. The Centers would be encouraged to study how to reduce disparities in demand for, access to, and use of cancer communications by ethnic minorities and underserved populations.

An important component of the Cancer Communications Centers of Excellence initiative is to develop practical tools ("toolkits") for the dissemination of cancer communications. Toolkits for the public, patients and their care givers, advocates and underserved populations will include practical and easy-to-use educational tools to improve the quality and availability of cancer communications. An evaluation component is included in these strategic communication efforts to identify effective cancer information delivery strategies. Evaluation techniques including focus groups, omnibus surveys, in-depth telephone interviews, and bounce-back card analyses will allow NCI to gauge the knowledge, attitudes, and behaviors of minority and underserved audiences in order to focus program efforts and develop effective messages.

The NCI-sponsored Minority Based Community Clinical Oncology Program (MBCCOP) provides for the establishment of partnerships between the NCI-supported research programs and community-based health service providers. It allows community hospitals and doctors offices to enroll patients onto NCI sponsored clinical trials. This program has always fostered collaboration between the NCI and medical

institutions serving ethnic minority and medically-underserved including rural populations. The Institute has used the MBCCOPs to study the dynamics of accrual of low-income individuals to clinical trials.

Item

Urological Cancers -- The Committee is pleased with the new initiatives in prostate cancer now underway; however, research in other urologic cancers such as kidney and bladder cancer needs to be enhanced. The Committee urges NCI to develop a plan to expand its research programs for other urologic cancers and take advantage of new knowledge that has been acquired about cancer diagnosis and treatment. (p. 60)

Action taken or to be taken

In collaboration with the National Institute of Diabetes, Digestive and Kidney Disorders, the NCI will establish a Progress Review Group (PRG) in FY 2001 to assist in setting priorities for research on kidney and bladder cancers. Like other PRGs, this PRG will be composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion early in FY 2002 and NCI's implementation plan is scheduled for completion in May 2002.

Scientists at NCI have developed exciting and dynamic research methods in order to improve the detection, diagnosis and treatment of urological cancers. The following precis gives a brief explanation into studies that are currently underway. These combined efforts, many of which are collaborations, will help scientists in their efforts to understand the molecular genetics of urological cancer, and uncover ways to improve the treatment and lives of these patients.

Kidney Cancer

About 31,200 people are expected to be diagnosed with kidney cancer in 2000 and an estimated 11,900 people with kidney cancer will die. Kidney cancer includes cancers of the renal cells, the main part of the kidney, and the renal pelvis, the lower part of the kidney where urine collects before entering the ureter and continuing to the bladder. About four-fifths of the kidney cancers occur in the renal cells, the main part of the kidney. The incidence and mortality rates are higher for men than women with men making up 60 percent of the cases and deaths attributable to kidney cancer.

For both types of kidney cancer, the only well-established risk factor is cigarette smoking. Compared to non-smokers, smokers have about twice the risk for renal cell cancer and about four times the risk for renal pelvis cancer than non-smokers. Other probable risk factors include obesity and, especially for renal pelvis cancer, heavy long-term use of analgesics, medications used to relieve pain. Cessation of smoking is the best single step in preventing these cancers. It is estimated that this measure alone would reduce renal pelvis cancers by one-half and renal cell cancers by one-third.

NCI has provided significant, long-term commitment to the study of kidney cancer, both extramurally and intramurally. Intramural scientists at NCI initiated studies in the early 1980's to identify the genes that cause cancer of the kidney. These studies led to the identification of the von Hippel-Lindau (VHL) gene, the gene for the hereditary and sporadic form of clear cell kidney cancer, the most common form of kidney cancer. A new type of hereditary kidney cancer, Hereditary Papillary Renal Carcinoma was described at the NCI and the gene for HPRC (the c-Met oncogene) was identified in 1997. NCI scientists are now studying a third form of hereditary kidney cancer, that associated with Birt-Hogg-Dubé Syndrome and are working to identify the BHD gene.

Intensive study is being carried out on the VHL kidney cancer tumor suppressor gene and the c-Met gene in order to understand how damage to these normal genes turns them into cancer genes. It is hoped that understanding the pathways of these cancer genes will lead to the identification of new targets for therapy of kidney cancer.

As stated earlier, many risk factors, including tobacco smoking, have been associated with human kidney cancers in population-based epidemiological studies. Confirmation of these causes, and establishment of detailed mechanisms that can be targeted for prevention and therapy, are hampered in human studies by numerous host, dietary, and environmental variables. Animal studies help overcome these limitations and permit direct examination of the cause-effect relationship between risks and kidney cancer development and tests of therapies directed at primary tumors. One of NCI's laboratories has been studying clear cell kidney carcinomas in rats; these are pathologically very similar to the most common kind of kidney cancer in humans and are thus a good model for study. Recently the laboratory demonstrated in such rat kidney tumors, for the first time, the presence of mutations in the VHL tumor suppressor gene, caused by a chemical found in tobacco smoke. Other types of rat kidney cancers, also found in humans, showed a reduced expression of the VHL protein. Since VHL alterations are frequently observed in human kidney cancer, these animal models provide a molecular mechanism linking tobacco smoking to the causation of kidney cancer in humans. This NCI laboratory expects to pursue this model to obtain a complete characterization of this risk situation, and to examine other known risk factors, such as obesity and hypertension, in the development of kidney cancers. Chemopreventive strategies can be explored, and the model can be used for molecular therapies targeting the VHL gene.

For full utilization of this animal model to help prevent and treat human kidney cancer, it is important to understand at a cellular level how VHL contributes to kidney cancer development. What goes wrong when the gene is mutated, or its protein is not expressed? These issues are poorly understood and are being actively pursued. A matter of fundamental importance is localizing the VHL protein within the cell. In studying this in kidney, NCI scientists made a recent and surprising discovery that the protein is localized in the mitochondria. These organelles provide energy-containing molecules for the cell, have a key role in controlling whether damaged cells die before they become cancerous, and are often abnormal in kidney cancer. This exciting discovery confirms that VHL may be an excellent target for kidney cancer prevention, intervention and therapy. Investigators now know where to focus their efforts in locating the key damage points in the cell caused by altered or absent VHL protein. Currently,

investigators are searching out reactions in the mitochondria controlled or influenced by VHL, and transfecting normal and mutant VHL into kidney cells in culture to observe the consequences for mitochondrial function, controlled cell death, and other parameters that directly influence cancer development.

All patients with newly diagnosed renal cell cancer can appropriately be considered candidates for clinical trials when possible. There are currently 51 open clinical trials in renal cell cancer in NCI's PDQ database of which NCI is supporting 35 of them. Most of the trials focus on finding improved treatments for advanced kidney cancer and include investigations in cancer vaccine therapies, chemotherapies, biological therapies and stem cell transplantation, either alone or in combination with other types of treatment.

In a recent and very promising Phase I/II study using allogeneic stem cell transplantation at NIH, scientists at NHLBI, NCI and the Clinical Center observed that 10 of the 19 patients with advanced kidney cancer had complete or partial regression of widespread tumors with treatment. The investigative approach used blood stem cells transplanted from a healthy sibling and the response rate of greater than 50 percent in patients with treatment-resistant disease is considered remarkable, considering that current first-line therapy is effective in less than 20 percent of cases. Three patients (16 percent) had total regression and seven (38 percent) showed partial regression.

However, the study was not without complications. The major side-effect, acute graft vs. Host disease, was usually of mild to moderate severity, and occurred in 53 percent of the patients. Two patients died due to transplant-related complications. Also, two patients that showed a response to the therapy have since developed progressive disease. Although follow-up in the study has been relatively short, there was a trend toward a survival advantage in those patients who had tumor shrinkage following the procedure.

In another NCI study, a new form of minimally invasive surgical therapy is being evaluated in patients with hereditary renal carcinoma. Called Radiofrequency Interstitial Tissue Ablative (RITA) therapy, this approach uses a modified surgical electrocautery to use heat to destroy tissue. The study's objectives are to evaluate the effectiveness of this therapy in destroying or slowing tumor growth in localized renal cell cancer, and to assess the toxicity, or side effects, to the patients of this treatment. If this form of therapy is successful with these patients, it will be evaluate in patients with sporadic (non-inherited) forms of renal carcinoma.

There is an intensive program to study the role of immunotherapy for patients with advanced kidney cancer. The current FDA approved drug for patients with advanced kidney cancer, IL-2, was developed at NCI. Both extramural and intramural scientists are evaluating different regimens and methods of administrating IL-2 based therapies in patients with kidney cancer. Also, new forms of anti-angiogenic therapies, which uses a family of drugs called angiogenesis inhibitors to prevent the growth of new blood vessels in solid tumors, are also being evaluated in patients with advanced kidney cancer.

Another new form of immunologic therapy, called mini-transplant therapy, is being evaluated in patients with advanced renal cell carcinoma. The early results of this therapy are encouraging and it is being evaluated in a larger number of patients. A new form of vaccine therapy, involving the VHL gene, is also being evaluated in patients with advanced kidney cancer.

Bladder Cancer

Over 53,000 individuals will be diagnosed with bladder cancer in 2000 and an estimated 12,200 patients will die from this disease. Bladder cancer is clinically and histologically diverse and patients seek medical attention with a variety of symptoms such as blood in urine (hematuria), inability to control the urge to urinate (urgency) or even pain. Urologists are the primary referral for the work up and management of bladder cancer and for most cases of bladder cancers, the only physician closely associated with this disease is the urologist.

Bladder cancer occurs in two forms, superficial (not into the muscle of the bladder) or invasive (into the muscle of the bladder) and each carries a different prognosis and treatment. Superficial bladder cancer is by far the most common type (approximately 80 percent of cases) and is generally not fatal since over 95 percent of patients with superficial disease live at least 5 years after effective treatment. Superficial cancers may be solitary or multiple and usually protrude into the bladder lumen connected by a fibromuscular stalk to their blood supply and the rest of the bladder. Often these are low grade papillary lesions, however, a small percentage can be high grade and are associated with muscle invasive bladder cancer. This form of high grade superficial bladder cancer is not papillary but flat and is referred to as carcinoma in-situ (CIS). Treatment for superficial bladder cancer is removal of the tumors using an endoscopic instrument called a cystoscope. Cystoscopy is performed by a urologist either in the office or in the operating room and allows visualization of the entire lining of the bladder (urothelium) for presence of tumors or suspicious lesions. If a tumor is seen, it is removed entirely and the area fulgurated (tissue destroyed using an electric current). In many cases, this is curative; however, 60-70 percent of superficial tumors will return requiring additional cystoscopic evaluations and biopsies. More worrisome regarding superficial tumors is the progression to the much more lethal muscle invasive tumor. Progression is directly related to the grade of the initial lesion and the CIS lesion is the most associated with muscle invasive disease and therefore carries a much higher risk when diagnosed.

Muscle invasive disease is highly associated with lymph and vascular invasion and ultimately metastatic disease. Up to 50 percent of patients with muscle invasive bladder cancer will develop metastasis and die of this disease. However, the prognosis of muscle invasive disease ultimately depends on the final pathologic stage of the cancer obtained after a radical cystectomy and lymph node dissection. Organ confined disease and no evidence of lymph node involvement carries an excellent prognosis with well over 80 percent of patients living at least 5 years. The presence of disease outside of the bladder decreases survival and gross involvement of the lymph nodes is also a poor prognostic finding. Once bladder cancer has left the bladder via a lymphatic or hematogenous route (metastatic disease), non-surgical treatment such as chemotherapy must be used. The standard chemotherapeutic regimen has been a combination of drugs known as M-VAC. Recently other less toxic regimens are being evaluated with acceptable initial results. However, radical cystectomy remains the best chance for cure in patients

with clinically localized bladder cancer with chemotherapy as an adjuvant therapy for patients at increased risk for recurrence and/or nodal involvement.

Over the last year, intramural scientists at NCI have focused research on the expression of mismatch repair (MMR) genes in the three most common urologic malignancies; prostate, bladder and kidney. Mismatch repair genes are important in the prevention of cancer by correcting potential mutations in other genes that are more directly involved in tumorigenesis. Alterations in expression of the two most commonly mutated genes, hMSH2 or hMLH1 may be important in initiation or progression of urologic malignancies. NCI scientists have identified an inactivating hMSH2 mutation in the prostate cell line, LNCaP, in addition to microsatellite instability and loss of hMLH1 expression in three of eighteen high grade renal cell carcinoma cell lines developed at NCI. Interestingly, no mutations in these genes have been identified in the bladder cancer cell lines or bladder tumors screened to date. The lack MMR mutations in bladder cancer may be due to the low number of cell lines and tumors screened and/or to a very low prevalence of inactivation of these genes in this particular tumor type. Moreover, bladder tumors have an overexpression hMSH2 and this finding has led to the use of hMSH2 gene expression as a marker for tumor recurrence in patients with bladder cancer. The overexpression of hMSH2 is detected in cells obtained from bladder washes in patients at risk for bladder cancer and correlated to the presence or absence of a bladder tumor. In an initial study of 32 patients, the results were promising and a more extensive study is currently in progress to fully elucidate prognostic implications of increased hMSH2 expression in bladder washes in patients at risk. Finally, NCI scientists are looking at developing an interdisciplinary, collaborative effort to develop a treatment protocol for patients with metastatic transitional cell carcinoma.

Additionally, in 2000, NCI researchers published a meta-analysis examining the interaction between smoking and a polymorphism in N-acetyltransferase-2 (NAT2), a gene involved in the metabolism of several carcinogens. NAT2 codes for an enzyme that detoxifies aromatic amines, compounds known to be potent bladder carcinogens present in tobacco smoke. Although the link between bladder cancer and smoking is well established (it is estimated that cigarette smoking accounts for about half of the bladder cancer cases in men and for about 30 percent in women), the relationship between smoking and bladder cancer risk was about 30 percent stronger among people with a particular polymorphism in NAT2 compared with those without the alteration. In an ongoing collaborative study with NIOSH, NCI is evaluating the influence of genetic factors on bladder cancer risk among Chinese workers exposed to benzidine, an established bladder carcinogen.

During the past 3 decades, scores of bladder cancer studies have suggested more than 40 high-risk occupations, yet the specific exposures responsible for these excesses remain largely unknown. The NCI is currently conducting an interdisciplinary, hospital-based case-control study of bladder cancer in Spain in areas with heavy concentrations of industry exposure to suspect bladder carcinogens. The purpose of this study is to clarify the etiologic role of suspect occupational bladder exposures including diesel exhaust, PAHs, oil mist, solvents, asbestos, and aromatic amines and their derivatives (e.g., MBOCA, dichlorobenzidine, orthotoluidine, magenta, auramine, azo dyes). Several non-occupational exposures also will be evaluated including cigarette smoking, phenacetin-containing analgesics, dietary

factors, urinary tract infections, urination frequency, urine pH, fluid intake, and air and water pollution. Collection of biologic specimens will permit evaluation of genetic susceptibility markers (e.g., NAT1, NAT2, and GSTM1) in relation to risk of bladder cancer, as well as their potential interactions with epidemiologic risk factors.

The NCI is initiating a population-based case-control study of bladder cancer in New Hampshire, Maine, and Vermont, to uncover the reasons for the high mortality and incidence rates that have persisted over several decades in this region. A previous NCI study conducted in Vermont and New Hampshire in the early 1980s suggested that only part of the excess risk in both sexes could be explained by exposures in the textile and leather industries, which were prevalent earlier in the century. The persistently elevated incidence/mortality rates for bladder cancer among both men and women in this region, despite the departure of high-risk industries decades ago, suggest that the role of non-occupational etiologic factors deserves further study. The purpose of this study is to determine the factors that contribute to the high risk of bladder cancer in the northeastern U.S. Arsenic in drinking water is one suspect exposure that may explain the New England bladder cancer excess. Although ingestion of high levels of arsenic appears to be a risk factor for bladder cancer, the effects of low to moderate levels of exposure, which seem to occur in the high-risk areas of the northeastern U.S., are unclear. The contribution of other risk factors will also be examined, including water contaminants other than arsenic, dietary factors, ethnicity, urinary tract infections, urinary stasis, urinary pH, occupational exposures, residential proximity to industrial sites, tobacco use, and genetic susceptibility and gene-environment interactions.

Xenograft Animal Models of Urogenital Cancers

A greater understanding of the biology urogenital cancers (prostate, kidney, and bladder) is needed. A major limitation to progress in this area of cancer research is the lack of well defined animal models. Animal models provide the most relevant systems to study the growth and spread of cancers. These models are of significant value in understanding the biology of cancer and evaluating novel treatment strategies for cancers. Two broad categories of mouse models are currently used in cancer research. The first, referred to as xenograft models and discussed in this section, uses the mouse as a host for human cancers, while the second studies mouse cancers that develop in mice. Xenograft models offer the opportunity to study actual human cancers while mouse tumors allow the study of cancer and its interactions with its natural host. It is important that the strengths of both model systems be used to study and understand cancer.

We have recently initiated a multi-disciplinary approach to develop and characterize relevant xenograft models of urogenital cancers. In an attempt to produce the most relevant and therefore valuable animal models the approach of orthotopic tumor implantation is being utilized. The failure to early work using xenograft models of cancer was the lack of orthotopic tumor implantation. Orthotopic tumor implantation involves the surgical implantation of human tumor fragments (obtained at the time of surgery) into the organ in the mouse from which the original human tumor was removed. For example if a prostate tumor is removed from a patient, that tissue will be implanted into the prostate of a mouse

using micro-surgical techniques. We have found that by using orthotopic tumor implantation the resultant xenotransplant models more closely resemble the human condition and therefore are more useful in the study of the cancer.

Our initial work with the orthotopic xenotransplant models has yielded tumor growth and early tumor models for renal and prostate, including a hereditary renal cancer that has not before resulted in a xenograft model. Using orthotopic prostate cancer models, we have extended our understanding of genes that may allow prostate cancers to spread and move to other parts of the body. Our continued efforts in this area of xenograft development will be of great value to our ongoing efforts in the research of urogenital cancers.

NCI held an international workshop on superficial bladder cancer in September 2000. This "State-of-the-Science" workshop brought together clinical bladder cancer experts and experts on molecular biology, cell signaling, new agent development, biomarkers, and clinical trial design, from North America and Europe, as well as patient advocates and scientists working in the pharmaceutical and biotechnology industries. The workshop included discussions on strategies for expediting progress in therapy of superficial (non-invasive) bladder cancers, strategies for preventing invasion and progression, obstacles to progress, and new molecular and other targets for therapy, and other new opportunities for progress. All presentations, discussions, and recommendations that emerge from this workshop are being made available to all investigators and to the public at large on various NCI websites, so that they may assist everyone working to conquer this disease. This information, along with the information from five other State of the Science workshops held for other cancers as of September 2000, can also be accessed at NCI's State of the Science (SOTS) website (http://www.conference-cast.com/webtie/sots/sots.htm).

FY 2001 Senate Appropriations Committee Report Language (S. Rpt.106-293)

Item

Behavioral science research -- The Committee commends NCI for expanding its infrastructure to fund behavioral and population research in cancer prevention, treatment, and control. NCI is encouraged to expand its investigation of the effective provision of mental health services to improve the course of cancer treatment and to aid in the adjustment to cancer survivorship. NCI is also encouraged to build upon its collaborations with the National Institute on Drug Abuse to more thoroughly investigate issues of youth tobacco use. In particular, the Committee is interested in expanding health promotion research focused on children and youth, and interdisciplinary research on tobacco addiction and cessation. The Committee also encourages NCI to expand its research on adherence to treatment regimens and to health-promoting behaviors such as physical activity and healthy diet. (p. 116)

Action taken or to be taken

NCI's Behavioral Research Program has been in existence for 3 years. The continued expansion of this program exemplifies the importance of behavioral science research as one of the foundations of effective cancer control. The program's mission is to initiate, support, and evaluate a comprehensive program of

behavioral research ranging from basic behavioral research to research on the development, testing, and dissemination of disease prevention and health promotion interventions in areas such as tobacco use, cancer screening, dietary behavior, and sun protection. The goal is to increase the breadth, depth, and quality of cancer prevention and control behavioral science. To realize this goal, the NCI has expanded collaborations with other NIH Institutes and agencies that support behavioral science research. NCI's strengthened commitment to behavioral science research is evident by the designation of Cancer Communications as well as Tobacco/Tobacco-Related Cancers as extraordinary opportunities for investment, which are among the highest scientific priorities of the Institute.

NCI's scientific priority in Cancer Communications is grounded in behavioral research. The goal of this broad set of initiatives is to increase the use of cancer communications by the public, consumers, patients, survivors, and health professionals - with a special focus on diverse populations - to accelerate reductions in the U.S. Cancer burden. Several of the objectives are being led by the Behavioral Research Program's Health Communication and Informatics Branch, including the development of a national biennial survey to assess information needs and national trends related to cancer communications.

NCI's scientific priority in Tobacco and Tobacco-Related Cancers also involves behavioral research, ranging from basic biobehavioral research to community-level interventions. The Behavioral Research Program's Tobacco Control Research Branch is leading this extraordinary opportunity, with broad participation and support from the entire Institute. The successful reorganization and integration of the NCI's tobacco control research efforts were manifested by a significant presence at the recent 11th World Conference on Tobacco OR Health, and a number of significant research initiatives noted below.

Program Accomplishments

The NCI has committed substantial resources, both personnel and fiscal, to the Behavioral Research Program (BRP). Through successful recruitments the NCI has increased, strengthened, and broadened behavioral science expertise on its staff, and will continue to do so. In the short time since the creation of the BRP, NCI has launched numerous initiatives targeted to both new and established behavioral science investigators using Requests for Applications (RFAs), Program Announcements (PAs), Supplements, and Career Development Awards. Many of these are listed below.

$ Transdisciplinary Tobacco Use Research Centers: In FY 2000, seven new research centers began to focus on a range of issues from biological and behavioral factors in tobacco use and nicotine addiction to the prevention of tobacco use among youth of diverse cultures. The Centers are jointly managed with the National Institute on Drug Abuse, with an additional large investment by the Robert Wood Johnson Foundation. Scientists from the seven centers have met with staff from the NCI, NIDA, and RWJF to identify cross-cutting issues, form working groups, examine barriers to research proposals, and enhance cross-site collaboration.

$ Research in State and Community Tobacco Control Interventions RFA: Twelve grants to conduct community-based research on policy and media interventions were announced in FY

2000. This RFA will be reissued, with plans to fund up to ten additional projects to test the most effective ways to reduce tobacco use at the state and community level.

$ Review and Analysis of Tobacco Industry Documents Program Announcement: Four grants were awarded in FY 2000 to facilitate a systematic, comprehensive analysis of scientific and marketing documents released by the tobacco industry that will help researchers develop strategies to reduce tobacco use. Four grants were awarded in June 2000 under this initiative to the Roswell Park Cancer Institute, the Massachusetts Department of Public Health, the University of California San Francisco and the Michigan Public Health Institute. The range of objectives include to: index, abstract, and evaluate documents and make them available to the public; improve scientific knowledge about the toxic and addictive properties of cigarettes; analyze documents to determine how the tobacco industry seeks to influence scientific process, policy making, community groups and the media, and young adults to recruit and solidify new smokers; and analyze the depositions and trial testimony for tobacco lawsuits filed in the United States during the 1990s to assess areas such as nicotine addiction, health consequences, tobacco product design and manufacturing, advertising and promotion, youth smoking initiation, and tobacco use cessation.

$ Basic Biobehavioral Research on Cancer-Related Behaviors RFA: Through the first issuance in 1998, eight applications were funded. Recently, this initiative was revised and reissued to target a broader applicant pool and to encourage proposals in diverse areas of cancer-related behavior. Six more applications were funded, several in the area of biological factors related to smoking cessation, and several related to stress/psychological functioning and the impact of these factors on the immune system. These grants should provide new knowledge about how people become addicted and the mechanisms by which stress might affect the immune system.

$ Small Grants Program for Behavioral Research in Cancer Control (R03): This initiative is facilitating the growth of a nationwide cohort of new scientific investigators with a high level of research expertise in behavioral cancer control research. Ten grants were funded in FY 2000 that focused on behavioral science issues.

$ Exploratory Grants for Behavioral Research in Cancer Control (R21): This is a new initiative to encourage pilot projects or feasibility studies to support creative, novel, high risk/high payoff research to accelerate advances in behavioral science. Six grants focusing on behavioral science have been funded since the R21 mechanism was initiated.

$ Health Communication in Cancer Control RFA: Five grants were funded from this RFA. These grants focused upon communicating genetic test results to families, tailoring communications for colorectal cancer screening, developing innovative strategies for adherence to nutrition recommendations, enhancing effective cancer communications for Latino women, conducting culturally tailored cancer prevention in African American women, and creating computerized symptom reporting systems for cancer patients. These grants should lead to new programs for

communicating with diverse groups.

- **$** NCI's Media Technology/Health Communication SBIR Grant Program: This program provides funding for investigators to develop novel interactive health applications using multimedia technologies to reduce cancer risks, provide treatment options, or meet the needs of cancer survivors.

Also, in the Administrative Supplements to Cancer Centers for Support of Family Research, NCI funded ten grants to identify the problems cancer causes for families and develop pilot interventions to help families cope with the burden caused by cancer. This is the first time NCI committed funds specifically to focus on the family impact of cancer. The first meeting of all funded investigators and other experts in family response to medical illness occurred in October 2000 to determine the most needed areas of research related to the impact of cancer on the family. Nine of the ten projects focused on families of adult cancer survivors or those at high risk for cancer and one grant focused on the families of pediatric cancer survivors. The mean age of adult patient samples was 61 and the mean age of family members was 51 with an age range from 11-67. Cancer sites were widely represented among the projects including prostate, breast, colon, pediatric, brain, and head and neck. Two projects had 50 percent minority accrual. All other project recruitment was regionally representative.

NCI has also substantially expanded opportunities for training for behavioral scientists with cancer-related interests. NCI's new R25 Cancer Education and Career Development Program supports the development of interdisciplinary training programs that provide behavioral scientists with the necessary knowledge and skills to conduct cancer-related research. NCI supports the newly revised K23 Mentored Research Career Development award, which is open to clinical psychologists and other clinically oriented behavioral scientists. This mechanism complements the NCI's K07 Career Development Award in Cancer Prevention, Control, and Population Sciences, which is being promoted to behavioral scientists through advertisements in relevant publications. Behavioral scientists who have completed their doctoral training and mentored experience are eligible for the new NCI K22 Transition Award, which provides support to investigators who are moving from a mentored to an independent research position. This award is expected to increase opportunities for behavioral scientists who are seeking faculty positions at our nation's leading cancer research institutions. The K05 mechanism is also available for mid-level to senior behavioral scientists. Thus, funding for the most productive and recognized behavioral scientists to devote substantial time to cancer-related research is now available.

5-A-Day Program/Health Promotion Activities: Behavioral researchers in nine academic sites collaborated with the NCI to publish detailed evaluations from the 5-A-Day community research projects. Each project showed significant, positive results in increasing fruit and vegetable consumption in the targeted audiences. The NCI and the American Cancer Society (ACS) are collaborating to disseminate and evaluate a successful church-based nutrition education program for African-Americans. In addition, 12 grants are supporting work in skin cancer prevention. The first annual conference of skin cancer prevention researchers will focus on identifying research needs in this area. NCI co-sponsored with the NIH Office of Behavioral and Social Sciences Research an RFA focusing on innovative approaches to disease prevention through behavior change. The behaviors of interest include tobacco

use, exercise, diet, and alcohol abuse. Finally, an in-house scientific group is currently reviewing epidemiological and behavioral evidence in the areas of diet, physical activity, and weight, and has recently released a report that includes recommendations for future scientific initiatives. NCI also is collaborating with the Agency for Healthcare Research and Quality (AHRQ) to conduct a synthesis of the research evidence on the effectiveness of behavioral interventions for dietary change. In the next year, we expect to have new initiatives in the area of diet, weight and physical activity.

NCI's Office of Cancer Survivorship

As the fight against cancer progresses, there are growing numbers of cancer survivors. It is estimated that there are currently over 8.4 million individuals alive today with a cancer history. Among adults newly diagnosed with cancer, over 60 percent can expect to be cured of or to live for 5 years or more with their illness. For children diagnosed with cancer this percentage is even higher, averaging 70 percent but reaching as high as 93 percent for specific cancers (e.g., Wilm's tumor). Current trends toward earlier diagnoses and more effective treatments, combined with the aging of the population, suggest that the number of survivors will only increase over the next 5 years. By the year 2010, it is expected that one out of every 250 adults aged 20-29 will be a survivor of childhood cancer. For these reasons, understanding the impact of cancer on survivors' lives and developing effective means of reducing the negative medical and psychosocial sequelae while enhancing function and quality of life has become an important goal for researchers to address.

The Office of Cancer Survivorship (OCS) is a strong and active supporter of research that focuses on the impact of cancer on survivors. Over 80 grants at the NCI focus on the impact of cancer on survivors' lives and enhancement of function and quality of life. In addition, pilot studies are planned to examine survivors' communication needs for supportive services and interventions in the community. A supplemental mechanism for cancer centers and the Special Populations Networks to examine survivorship needs among underserved groups is in preparation. The Community Clinical Oncology Programs network also supports smoking cessation research that uses a combination of behavioral/educational interventions and pharmaceutical interventions.

Since last year, the OCS, in conjunction with members from NCI's Surveillance Research and Applied Research Programs, has been involved in several efforts to generate descriptive profiles of the survivorship community. In the first of these efforts, the OCS developed a descriptive profile of the demographic, clinical, and survival characteristics of breast cancer survivors diagnosed over a 24-year period in nine SEER areas in the U.S. These data confirmed already reported improvements in 5- and 10-year relative survival by decade. Additionally, relative survival by decade of diagnosis was compared across married and unmarried survivors. Findings indicated improved survival rates for married survivors for each decade, reflecting the possible role of social support or economic advantage in better outcomes. Profiles of survivors of other common cancers will be summarized in separate papers.

There is growing concern over the hidden cost of survivorship on families, in particular with respect to the impact of cancer on the health, psychological well-being, and economic status of other family

members. OCS staff are examining the published research on family functioning across the illness and developmental continuum: from being at risk for cancer; to being a parent of a childhood cancer survivor, a partner of a survivor, the adult child of a survivor or the aging family member of a survivor. Currently, the OCS is working with National Health Interview Survey (NHIS) data to determine the impact of cancer survivorship on the family. This will be done by determining the estimated prevalence rates of families affected by cancer in the NHIS, and examining the demographic characteristics of these families. In recognition of the importance of family both on survivors' well-being and vice versa, the OCS held workshop in Fall 2000 for some of its family research grantees to share study findings and think about directions and resources needed to develop research in this critical area. It is expected that the results of this meeting will contribute to a possible future RFA on family adaptation to cancer.

New Directions

In the next year, NCI will issue announcements in several new areas.

$ Centers for Population Health: Understanding cancer-related health disparities requires a broad perspective that integrates many disciplines and includes a focus on social determinants, such as cancer. NCI is planning to issue an RFA for Centers in this area in order to have a major population level impact on cancer. We are exploring co-sponsorship with other NIH institutes and a major foundation.

$ Centers of Excellence in Cancer Communications: The 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.

$ Smoking Cessation: We have begun discussions with NIDA about the creation of a clinical trials group for smoking cessation research.

$ Expand behavioral research within the Community Clinical Oncology Program.

Item

Bone disease -- The Committee encourages the National Cancer Institute to study the role of angiogenesis, i.e., the growth of new blood vessels, in metastasis of breast and prostate cancer to the bone. In addition, the Institute is encouraged to develop experimental genetic animal models that replicate the process of human cancer metastasis to the bone in humans, and to explore why bone is a preferential site for metastases. (p. 116-117)

Action taken or to be taken

Please refer to pages NCI-38 through NCI-40 of this document for NCI's response to this significant item regarding Bone Disease.

Item

Breast cancer -- . . . . The Committee strongly urges the Institute to continue to expand breast cancer research and to devote the highest possible funding level to finding the causes and cures for this disease. (p. 117)

Action taken or to be taken

In 2000, an estimated 182,800 American women were diagnosed with breast cancer and about 40,800 women died from the disease. Breast cancer is the leading site of new cancer cases for women and, after lung cancer, the second leading cause of cancer deaths in women. Despite the significant advances in detection, diagnosis, treatment, and prevention, thousands of women continue to lose their lives to breast cancer each year. For these reasons, breast cancer research remains a high priority for NCI.

To assist NCI in identifying and prioritizing scientific needs and opportunities that are critical to facilitating progress against breast cancer, NCI established a Breast Cancer Progress Review Group (PRG) that assessed the state of the science, identified gaps in knowledge and research priorities, and made recommendations for moving the field ahead. The report of the NCI's Breast Cancer PRG, Charting the Course: Priorities for Breast Cancer Research, identifies a number of questions that still need to be answered and areas of research and care that need to be further addressed. NCI uses a portion of its grant funds to support high-priority applications relevant to breast cancer. We give special attention to applications that address high-priority gap areas as defined by the Breast Cancer PRG, particularly those that fall within the areas of extraordinary opportunity in the NCI's Bypass Budget but fail to meet the established payline. The complete report of the Breast Cancer PRG is available on line (http://osp.nci.nih.gov/PRGReports/BPRGReport/bprgtableofcontents.htm).

In addition to the Breast Cancer PRG, the NCI has solicited recommendations from other working groups focused on important areas of cancer research to assist the Institute in its strategic planning process. Through this planning process, the NCI has implemented a number of initiatives that are meant to strengthen the nation's cancer research infrastructure. The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2002 includes descriptions of these initiatives. The initiatives are not, for the most part, disease-specific, but address problems and opportunities common to all tumors and emphasize the development of technologies and approaches applicable to many cancers.

The portfolio of funded research projects in breast cancer is both broad and deep with over 1400 individual NCI-funded projects having relevance to breast cancer. In FY 2000, NCI expended over $400 million in research related to breast cancer.

To encourage translational research, in September 2000, NCI awarded $10.1 million in first-year funding to four breast cancer research groups under the Specialized Programs of Research Excellence (SPORE) funding mechanism. SPOREs are 5-year grants that support innovative, multidisciplinary, translational research which may have an immediate impact on improving cancer care and prevention. The first SPOREs in Breast Cancer were awarded in 1992. The four new awards bring the total

number of SPOREs focused on breast cancer to nine, with a total FY 2000 breast cancer SPORE funding of approximately $19.0 million. One of the new SPOREs will study the genetic aspects of breast cancer. Scientists will develop functional assays for known breast cancer susceptibility genes, look for new breast cancer susceptibility genes, use both cell lines and mice to understand the molecular biology of the disease, and develop inhibitors for genes involved in disease progression. Another SPORE will study the role of diet and hormones in the prevention and development of breast cancer. A third SPORE's projects include the development of molecular markers involved in the classification and progression of the disease, as well as molecular strategies to improve breast cancer detection, prevention, and therapy. One strategy will examine vaccines for prevention and another will study DNA demethylating and histone deacetylating agents for treatment of the disease. The fourth SPORE will focus on a broad range of breast cancer projects involving the development of chemoprevention agents, the mechanism of tamoxifen resistance, and new treatment options using gene therapy, DNA vaccines and radioimmunotherapy techniques.

Understanding the Biology and Etiology (Causation) of Breast Cancer

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

Over $85 million was spent in FY 2000 for research related to breast cancer genetics. In addition, NCI has made a major investment in epidemiologic studies designed to clarify breast cancer risk factors. Such studies are assessing the role that environmental and chemical exposures, including alcohol and tobacco, may play, as well as the potential etiologic importance of radiation, endogenous hormones, familial/genetic factors, and host/lifestyle factors such as physical activity and diet/nutrition. Of particular interest are studies on the role of various genetic variations, particularly among different ethnic groups, in the enzymes that metabolize steroid hormones or environmental agents. Other studies are attempting to improve techniques to measure exposures applicable to better defining breast cancer risk factors. Efforts include methods to better assess nutritional intake and physical activity, define the genetic epidemiology of breast cancer, evaluate gene-environment interactions, and predict outcomes following a diagnosis of breast cancer.

A number of research studies are addressing the higher breast cancer rates in various areas of the United States. These studies are examining the association of breast cancer risk with exposures to contaminated drinking water; indoor and ambient air pollution, including pesticide levels in household

dust; electromagnetic fields; and hazardous and municipal wastes.

Several recent studies suggest that some organochlorines (commonly used as pesticides) affect estrogen production or metabolism and increase mammary tumors in animals; human studies are inconsistent to date. NCI is conducting case-control and cohort studies in numerous areas that will address this question; chemicals that are being measured in human serum and adipose tissues are DDE, PCBs, and PAHs. NCI and CDC are jointly following a group of farm families accidentally exposed to high levels of PBBs during the 1970s to look at a variety of health outcomes, including risk for breast cancer. Five centers that are collaborating in research seeking reasons for the increased breast cancer rates in the Northeast/mid-Atlantic U.S. Are pooling data and analyses to investigate the role of organochlorine pesticides in breast cancer risk.

NCI has funded an initiative entitled "Geographic Information System for the Long Island Breast Cancer Study Project." A Geographic Information System (GIS) is a powerful computer mapping data management and analysis tool for integrating diverse sources of information that have one common element: they can be referenced to a location on the earth's surface. The purpose of this initiative is to develop, test, and document a GIS-based decision support system for investigating the potential relationships between breast cancer and estimated exposure to environmental contamination on Long Island. It will support both temporal and spatial research so that environmental factors and cancer risks can be examined as they vary over time and space.

Exposure to estrogen produced by the body clearly raises risk of breast cancer. Reproductive factors that may affect levels of estrogen and other hormones are receiving intensive study with regard to breast cancer risk. A recent re-analysis of over 90 percent of breast cancer studies throughout the world showed an increased risk for women who used hormone replacement therapy (HRT) for 5 years or longer. The risk was seen not only in current users, but also in women who stopped the therapy some time in the previous 4 years. No risk was seen in women who had stopped the therapy for more than 4 years. Most of the women in the re-analysis were on estrogen alone. Recent studies have shown the risk of breast cancer to be greater among women using combination estrogen/progestin, compared to estrogen alone. Both groups of hormone users had a higher risk of breast cancer than non-users. The risk increased with longer duration of use. After 5 or more years of non-use, the risk returned to that of non-users. Numerous studies are addressing estrogen metabolism, estrogen and progesterone receptor levels, and excreted estrogens for potential relationships to breast cancer risk.

The incidence rates of breast cancer are substantially lower in Asian countries than in the U.S. A possible explanation is that Asian women consume much greater amounts of soy foods than do Caucasian women. Isoflavonoids, present in soy foods, are structurally similar to estradiol. It is hypothesized that isoflavonoids may influence breast cancer risk. Overnight urine samples collected from women participating in a cohort study in China were analyzed for isoflavonoids. Levels of these isoflavonoids in the urine were substantially lower among women with breast cancer than controls. The result suggests that a high intake of soy food may reduce breast cancer risk and warrants further study as a potentially preventive intervention. Obesity, body mass index, body fat distribution ("apple" versus "pear"), weight change over the lifespan, and physical activity are being intensively studied for their

effect on breast cancer incidence, prognosis, and mortality. A broad range of dietary factors is also under study, with several projects focusing on unique dietary influences in ethnic and/or migrant groups, such as African American, Hispanic, Native Hawaiian, and Asian American women. Specific dietary/nutritional factors of interest include dietary fats, alcohol consumption, and caffeine. Vitamins and other antioxidants consumed in the diet are being studied for potential protective effects. Future questions of interest are whether specific dietary constituents that differ between ethnic groups can be shown to affect breast cancer risk, and methodologic studies are needed to improve the accuracy of our assessment of diet and of social and behavioral influences on dietary constituents.

The Cancer Genome Anatomy Project (CGAP) was initiated by NCI in 1997. CGAP develops genomic resources that support cancer research, diagnosis, and treatment. Since its inception, it has continued to compile a comprehensive index of genes associated with carcinogenesis; and has now identified more than 762,000 expressed sequence tags from cDNA libraries prepared from normal, precancerous, and cancerous tissues. Currently, CGAP is supporting the development of innovative technologies that enable investigators to elucidate profiles of gene expression. From such profiles, molecular markers are identified that will potentially advance clinical screening and early cancer detection. Currently, CGAP has identified 235 genes that are uniquely expressed in breast cancer tissues. These genes can be studied by both basic and clinical investigators in defining and characterizing the molecular profiles of breast cancer cells, with anticipated applications in diagnosis, treatment and screening.

The Early Detection Research Network (EDRN) was started in late 1999 and expanded in 2000. It brings together 31 institutions to search for and evaluate new ways of testing for early cancer and for cancer risk. Advances in cancer research, including programs such as the CGAP, have uncovered a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are turning cancerous. The EDRN will translate these discoveries into methods for detecting cancer at its earliest stages and identifying people at risk of cancer before they develop the disease. Seven of the institutions are focusing on breast cancer biomarkers and tissue.

NCI, along with the National Institute of Aging and the National Institute of Nursing Research, is supporting a program announcement that targets breast cancer research in a wide range of areas including: age-related factors in carcinogenesis, the relationship of repair and controlled cell death to cell senescence; age-related biological factors which can affect the initiation, promotion or treatment of cancer; investigating patterns of illness; and sociodemographic factors related to breast cancer prevention in older women.

The Cancer Genetics Network (CGN) established by NCI in 1998. It is a national Network of centers specializing in the study of inherited predisposition to cancer. The CGN consists of eight centers and an Informatics and Information Technology Group that provide the supporting logistics infrastructure. The Network supports collaborative investigations on: the genetic basis of cancer susceptibility, mechanisms to integrate this new knowledge into medical practice, and means of addressing the associated psychosocial, ethical, legal, and health issues. To accomplish these goals, it is creating a registry of individuals at high risk for cancer. These individuals may serve as probands for the identification of

families or as participants in other types of studies of cancer susceptibility. The Network will provide registry participants with relevant information about cancer predisposition and will facilitate access to studies focused on early detection and prevention. In its first 18 months, the Network has been implementing pilot projects, recruiting participants into the registry, and developing operating procedures.

The Cooperative Family Registry for Breast Cancer Studies (CFRBCS) was initiated in 1995, and represents a comprehensive and collaborative research infrastructure established to facilitate interdisciplinary studies in the genetics and epidemiology of cancer. The registry, which continues to grow, contains information and laboratory specimens contributed by more than 5,000 families who have a history of breast and/or ovarian cancer. This registry provides researchers with biological specimens with associated family history, clinical, demographic and epidemiologic data from participants and their relatives. The CFRBCS' repository is particularly suited to the support of interdisciplinary and translational breast cancer research.

NCI, along with NIEHS, NIOSH and EPA, issued a joint RFA that solicits investigator-initiated studies to investigate the relationship between the exposure of endocrine disruptor chemicals (EDCs) and adverse health effects in humans, including cancer development. EDCs are synthetic chemicals, used or manufactured in the workplace and released in the environment, that may cause adverse health effects by interfering with the function of the endocrine system. While it has been speculated that some endocrine-related diseases or conditions such as breast and prostate cancers are caused by EDC exposure no linkage has been established between exposure to a specific environmental EDC and adverse health effect in humans. NCI expects to support three to five new projects in FY 2002.

Detection and Imaging

Please refer to pages NCI-40 through NCI-44 of this document for NCI's response regarding detection and imaging.

Prevention

The National Surgical Adjuvant Breast and Bowel Project (NSABP), which receives its primary funding support from NCI, is conducting the Study of Tamoxifen and Raloxifene (STAR). This clinical trial is designed to see how the drug raloxifene (Evista7) compares with the drug tamoxifen (Nolvadex7) in reducing the incidence of breast cancer in women who are at an increased risk of developing the disease. Tamoxifen has been used for more than 20 years to treat patients with breast cancer. This drug works against breast cancer, in part, by interfering with the activity of estrogen, which promotes the growth of breast cancer cells. In October 1998, the U.S. Food and Drug Administration (FDA) approved tamoxifen to be used as a prevention-based treatment to reduce the incidence of breast cancer in women at high risk of the disease. FDA's decision was based on the results of the Breast Cancer Prevention Trial (BCPT), a study of more than 13,000 pre- and postmenopausal high-risk women ages 35 and older who took either tamoxifen or a placebo (an inactive pill that looked like tamoxifen) for up to 5 years. NSABP conducted the BCPT, which also showed that tamoxifen works

like estrogen to preserve bone strength, decreasing fractures of the hip, wrist, and spine in the women who took the drug. Raloxifene was approved by the FDA in December 1997 for the prevention of osteoporosis in postmenopausal women. It was shown to reduce the incidence of breast cancer in a large osteoporosis trial, the MORE study. Researchers with NSABP are conducting the study at over 500 centers across the United States, Puerto Rico, and Canada. As of the summer of 2000, over 6,000 participants, of the 22,000-participant goal, have been enrolled. One goal of the STAR study is to get a significant number of minority women to enroll. NSABP has taken several novel approaches to encourage minority women to participate. In addition, a recent analysis of nine NSABP clinical trials have shown that tamoxifen works equally well with Caucasian and African-American women.

The Breast Cancer Risk Assessment Tool is a computer program that women and their health care providers can use to estimate a woman's chances of developing breast cancer based on several recognized risk factors. The Breast Cancer Risk Assessment Tool also provides information on the drug tamoxifen. The risk factors included in the tool are: personal history of breast abnormalities, current age, age at first menstrual period, age at first live birth, breast cancer history of close relatives, whether a woman has had a breast biopsy, and race. Other risk factors for breast cancer have been identified or proposed, but are not included in the Breast Cancer Risk Assessment Tool for two reasons: either evidence that these factors contribute to breast cancer risk is not conclusive, or researchers cannot determine how much these factors contribute to breast cancer risk as precisely as with the factors listed above. Such risk factors include: age at menopause, dense breast tissue, use of birth control pills or hormone replacement therapy, a high-fat diet, alcohol, radiation exposure, and environmental pollutants. The Breast Cancer Risk Assessment Tool estimates a woman's risk of developing breast cancer for two time periods: over the next five years and her lifetime. The tool compares these risks (given as a percentage) to those of women of the same age with no risk factors other than their age, and the risk of women who were eligible to participate in the BCPT. Scientists at the NCI and the NSABP developed this tool.

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

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

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

Treatment

NCI has emphasized the importance of increased participation, by patients and doctors, in clinical trials if better approaches to breast cancer are to be rapidly developed. To facilitate enrollment, a multi-media approach has been developed that provides patients and physicians with multiple access points to clinical research. A user-friendly web site (http://cancertrials.nci.nih.gov) helps women consider whether to enter a clinical trial for the treatment of their cancer. Launched in May 1998, the web site quickly helps women and their doctors sort through the hundreds of research studies under way on breast cancer to find those of interest to them. The site is seamlessly linked to NCI's CANCERNET database that contains descriptions of over 300 clinical trials for breast cancer including 187 NCI-sponsored trials. Of these, 100 are Phase I trials in which novel approaches to dealing with breast cancer are being tested for safety and 23 are Phase III trials representing interventions that are closest to general medical practice. For those who prefer the phone or fax, NCI hosts 1-800-4-CANCER and is able to fax or mail information in the CANCERNET database, including educational brochures, in response to requests from patients and physicians.

Chemotherapy drugs use different ways to prevent tumor cells from dividing so they stop growing or die. A major research effort in the 1990's has been directed towards detecting whether extremely high doses of chemotherapy can produce cures for women with advanced or high-risk breast cancer. These high doses required transplantation of the patient's blood producing cells (autologous stem cells) in order to rescue the normal blood forming cells that are also destroyed by the high dose chemotherapy. Advances in supportive care (use of growth factors, anti-viral agents, improved cell transplants) have markedly reduced the death rate from the procedure itself from 15 percent in 1990 to about 1 percent currently. NCI has sponsored 4 national studies to determine if this aggressive approach can significantly improve survival. The first trial of women with advanced disease did not show an advantage compared to more standard doses. However, we are awaiting the results from 3 trials in women with high risk, but not metastatic disease. Two of the trials have completed their enrollment and it will be another 1-2 years before results are expected. Patients in the third trial are still being enrolled.

Finally, NCI, in collaboration with the NIH Office of Research on Women's Health, the National Institute on Nursing Research and the NIH Office of Medical Applications of Research, hosted a major international NIH Consensus Development Conference on adjuvant therapy of breast cancer. The meeting was held November 1-3, 2000 and brought together national and international experts to evaluate the results of breast cancer clinical trials from the last 10 years, many of which were sponsored

by NCI. Recommendations were made to physicians and patients selecting therapy for different types of early stage breast cancer. Adjuvant therapy – treatment used in addition to surgery to kill cancer cells that may have begun to spread to other organs – includes chemotherapy and hormonal therapy, typically tamoxifen. In addition to these systemic therapies, radiation therapy is sometimes used as a local adjuvant treatment to help destroy breast cancer cells that have spread to nearby tissues. Some key recommendations of the consensus panel included treatment with a combination of chemotherapy drugs improves survival and should be recommended for most women with localized breast cancer; for women whose tumors have estrogen receptors, hormonal therapy is recommended; and radiation treatment is recommended for women who have had mastectomies and are at high risk for recurrence of cancer.

Other Selected Activities Related to Breast Cancer Treatment Include:

Early Therapeutics Development with Phase II Emphasis: Through an RFP, NCI has funded a group of organizations or consortia with the capabilities and facilities to conduct Phase II and early clinical trials of NCI-sponsored agents, to evaluate biologic effects of these agents on their molecular targets, to evaluate other relevant biologic effects and to determine clinically relevant outcomes/correlates. The program has instituted a series of new trials that explore promising combination therapies, and high priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting.

Cooperative Group Phase III Trials: The Clinical Trials Cooperative Group program performs definitive, large-scale Phase III trials to determine whether new treatments actually improve upon the results seen with the current standard approaches. Presently, several new promising treatments are being evaluated. The addition of Herceptin, a monoclonal antibody that targets a receptor that contributes to tumor growth on the surface of the breast cancer cell, is being studied in women with node-positive breast cancer. Clodronate, a new bisphosphonate that has been shown to decrease the complications of bone metastases in women with advanced cancer, is now being tested in women with stage I and II breast cancer. In total, 20 Phase III studies are currently ongoing in the Cooperative Group program. If one adds to this the nine Phase II developmental trials currently ongoing in the Cooperative Group Program, this effort is clearly the largest single therapeutics development effort in the world for breast cancer treatment.

Therapeutic Modulation of Angiogenesis in Disease: The purpose of this co-sponsored initiative is to encourage the translation of basic knowledge of the angiogenic process into therapeutic applications. It may also promote new collaborations between basic and clinical scientists currently engaged in this area of research to design novel therapeutic approaches to disease.

Clinical Trials Restructuring: NCI and many of the clinical researchers it supports are re-engineering NCI's clinical trials program. The aim is to enrich the scientific input in clinical trials conception and design, streamline operations, and broaden access to participation in trials by both patients and physicians. Pilot studies are planned that will test new systems for realizing these goals. Breast cancer is one of the diseases targeted for inclusion in the Cancer Trials Support Units (CTSU). The CTSU will

serve as a "one-stop shop" to allow user access to NCI-supported clinical trials by physicians and patients. Uniform informatics will be developed to allow investigators in any cooperative group to participate in all breast cancer trials opened in the CTSU. The CTSU opened for patient enrollment July 2000. Patients and physicians can access the clinical trials currently available at the CTSU website (www. Ctsu.org). In addition, because the restructuring initiative encompasses multiple new programs, NCI has created a "gateway" website (http://cancertrials.nci.nih.gov/system) to enable the research and patient community to easily access specific websites related to programs of interest to them.

Item

Cancer and minorities -- The Committee remains concerned over recent statistics citing higher incidences of cancer among the native Hawaiian population. In comparison to other ethnic and racial groups, native Hawaiians have the highest incidence of the most common forms of cancer such as breast, colon, and lung cancer. The Committee encourages continued research in the areas of prevention and detection, utilizing nurse practitioners in community-based centers for screening and education for the underserved populations. (p. 117)

Action taken or to be taken

As part of the National Cancer Institute's (NCI) 5-year strategic plan to reduce cancer health disparities, NCI is expanding its research resource commitments to surveillance, epidemiology, and intervention research to elucidate the underlying causes for, and to design interventions to reduce, cancer health disparities experienced by special populations such as the Native Hawaiians. With respect to surveillance research, the state of Hawaii and significant areas in California (Greater Bay area of San Francisco and Los Angeles County) are part of the NCI SEER Program. For over 25 years, cancer incidence, survival and mortality data have been collected and reported on Native Hawaiians. The NCI SEER Program is in the process of developing an updated monograph on racial and ethnic cancer rates and trends. It will include recent cancer incidence and mortality rates for native Hawaiians as well as other specific racial/ethnic groups. Rates for a recent time period will be compared to earlier rates (centered on 1990) and trends noted. The publication should be available in Fall 2001.

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

- Hawaii: Infant Leukemia among High Birth Weight Infants
- Puna, Hawaii: Native Hawaiian Women and Breast Cancer
- Maui, Hawaii: Barriers to breast and cervical cancer screening among Native Hawaiians
- Honolulu, Hawaii: Spirituality among Native Hawaiian Cancer Survivors – Focus groups,

interviews, and chart review are being used to generate a model for understanding the role of culture and spirituality in cancer survivorship.

- Honolulu, Hawaii: Knowledge, Attitudes and Practices Regarding Breast Cancer among Native Hawaiians. Survey results 10 years apart are being compared to make recommendations for adjustments to cancer control and education programs, with particular attention to perceived barriers and motivators.

In FY 2000, NCI funded over $5 million in extramural epidemiological research projects in the state of Hawaii. This research explores a number of key cancer risk factors such as diet, cervical human papilloma virus infections, genetic susceptibility and colorectal adenomas, and the effects of soy on estrogens and mammographic densities. Given the great ethnic diversity within the state of Hawaii, studies comparing Native Hawaiians with state residents representing other ethnic groups play a key role in highlighting important cancer health disparities among different ethnic groups and suggesting intervention strategies to reduce these disparities.

With respect to primary prevention interventions, Native Hawaiians are part of a 5-year smoking prevention intervention study testing different strategies for activating multi-ethnic youth to resist taking up the use of tobacco.

Also in FY 2000, the NCI instituted the Special Population Networks for Cancer Awareness and Training to invest resources in building community-based infrastructure to support community-based participatory research and education. One of the Special Populations Networks awarded focuses on Native Hawaiians. The title of the 5-year, $2.5 million project is the " 'Imi Hale Native Cancer Research and Training Network," and the Principal Investigator is a part-Hawaiian oncologist. It will be housed within an already existing network known as Papa Ola Lokahi, which has responsibility for overall Native Hawaiian health on each island within the State, and serves as advocate and administrative umbrella for the five Native Hawaiian Health Care systems on each island. The overall goal of the project is to reduce cancer incidence and mortality among Native Hawaiian through a coordinating infrastructure to be known as 'Imi Hale, and to build capacity among Native Hawaiian communities in cancer awareness. Another aim is to initiate cancer research training and control activities among the population of native Hawaiians, including a goal to "Create programs and opportunities to increase the number of Native Hawaiian researchers through training of promising young students, graduates and physicians." Papa Ola Lokahi already provides support in the form of fellowships for training of Native Hawaiian health professionals and community members

Project plans include the establishment of a clearinghouse, a statewide inventory for assessment of all cancer awareness programs, and the use of mentors via collaborative partnerships, internship-matched training sites, technical assistance for grant writing, pilot studies to shape R01 applications in building research-training capacity for reversing cancer disparity rates among native Hawaiians. Collaborators for the project are the University of Hawaii Cancer Research Center, Kaiser Permanente Center for Health Research, State of Hawaii Department of Health, University of Hawaii School of Social Work, the Pacific Biomedical Research Center and the Native Hawaiian Center of Excellence, part of UH, and Tripler Army Medical Center. The project is partially based upon earlier programs--two research and

one cancer screening-- funded by NCI, the American Cancer Society, and the Health Resources and Services Administration.

The Cancer Information Service (CIS) is another NCI program that has a special emphasis on cancer information and education to Native Hawaiians. The CIS Partnership Program brings cancer information to organizations that reach people who traditionally do not seek health information. Partnership activities include a nationally coordinated, regionally focused program committed to reaching minority and underserved populations that do not have adequate access to health information and services. The CIS Partnership Program provides cancer information and program development assistance to organizations that reach people in particular need of cancer information and services, particularly minority and medically underserved audiences. CIS of the Pacific Region has a Hawaii Partnership Office, located at the Cancer Research Center of Hawaii. Partnerships with organizations serving Native Hawaiians have been long-standing, as the examples that follow illustrate.

CIS brings together leaders of the Native Hawaiian community and researchers at the Cancer Research Center of Hawaii (CRCH). CIS assists these partners in their efforts to identify and develop collaborative and participatory research opportunities that speak to the priorities/interests of the Native Hawaiian community. CIS facilitates the flow of information/education between the NCI, the CRCH, and the community in order to build institutional understanding and capacity to address research priorities, processes, and concerns.

For the ‘Imi Hale Project, mentioned previously, CIS has provided training, materials development/dissemination assistance, and regular updates regarding cancer control activities and opportunities at the local/national level. CIS will provide capacity building assistance in areas such as training, materials development, and promotions, in addition to serving as a member of their Strategic Planning Task Force.

CIS supports Hui No Ke Ola Pono, in their efforts to implement the Kokua Program, a program funded through a Rural Health Grant that provides breast and cervical cancer screening/education to Native Hawaiian women on the island of Maui. CIS provided breast/cervical cancer training for their staff, components of which addressed clinical trials, quality information available through the Internet, outreach strategies for culturally diverse populations, and information/resources available through the CIS. In addition, CIS has provided media training which was designed to help participants develop messages, utilize major/minor media resources, and negotiate with media to increase promotional capabilities.

CIS is a member of the American Cancer Society’s Native Hawaiian Subcommittee. Subcommittee efforts first focused on developing tools to reach Native Hawaiian women about the importance of breast care with culturally appropriate materials. CIS contributed to a training video for health care professionals – Caring for Native Hawaiian Women: Understanding Cultural Values in Treatment of Breast Health – designed to increase cultural sensitivity among providers and will lead a train-the-trainer program to accompany the video.

WEB Wahine: Surfing for Health, a research project developed by CIS, is an internet-based breast health education program targeting Native Hawaiian women in the rural areas of Waimanalo, West Hawaii, and West Kauai. Pending funding, the internet training sessions will be facilitated in a 'talk story' format with hands-on training for each participant. Women will be guided through quality breast health websites; in addition, supplementary breast health/cancer education materials from the NCI will be provided. The purpose is to provide a comfortable and interactive session for women to learn about the wealth of breast health information available through the internet. In the process, they will increase their awareness of breast health/cancer and improve their computer and web searching skills.
Item

Complementary and alternative cancer therapies -- The Committee expects NCI to work collaboratively with the National Center for Complementary and Alternative Medicine to support expanded research on promising complementary and alternative cancer therapies as well as on their integration with traditional therapies. Thousands of Americans are turning to these therapies and consumers will benefit from the rigorous scientific review of these therapies. The Committee would like to be briefed on the progress of the Institute's efforts prior to the next appropriations cycle. (p. 117)

Action taken or to be taken

The National Cancer Institute (NCI) and the National Center for Complementary and Alternative Medicine (NCCAM) have developed a close, collaborative relationship, which has resulted in the establishment of a variety of joint projects.

The NCI has for the first time initiated a program to encourage and support complementary and alternative medicine (CAM) at the NCI-designated Cancer Centers. This program solicits applications and performs a competitive review of pilot projects (basic and clinical) in any of a variety of CAM approaches. The research will be performed at comprehensive and clinical P30 cancer centers but it also encourages these centers to enlist 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 NCAAM. The NCI and NCCAM have each committed one million dollars per year over the next 3 years to support high-quality applications responding to this program.

The NCI was a co-sponsor of an NCCAM request for applications (RFA) for new centers for CAM cancer research. Several NCI-designated comprehensive cancer centers applied for these grants. Also, the NCI has participated in a number of CAM-related RFAs such one for Botanical Research Centers initiated by the Office of Dietary Supplements and one for Centers for MindBBody and Health Interactions initiated by the Office of Behavioral and Social Science Research. The NCI is responsible for administering the grant for one of the successful mind-body center applicants.

The prospective trial at Columbia Presbyterian Medical Center examining the effect of the "Gonzalez regimen" (a nutritional program with oral pancreatic enzymes and "detoxification" regimen) continues to be jointly supported by the NCI and NCCAM. Also a study of the use of oral shark cartilage in

combination with conventional chemotherapy and radiation in patients with advanced, non-small cell lung cancer began accruing patients in April 2000. The NCI and the NCCAM are jointly sponsoring this study.

The NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) has made the Best Case Series Program a high-priority. This program affords opportunities for alternative medicine practitioners to provide information about patients with cancer treated with alternative medical approaches. The medical records and primary source materials (medical imaging studies and pathology specimens) are sent to the OCCAM which checks for completeness of the data, arranges the review of the radiology and pathology, summarizes and presents the materials to the CAPCAM for review. This ongoing program has recently been advertised to the CAM practitioner community. The NCI's interest in receiving submissions to this program is being disseminated via direct mailings to CAM practitioners, sessions at CAM conferences and notices and articles in CAM and conventional journals and magazines.

In the arena of Cancer CAM information, NCI and NCCAM collaborated to co-sponsor with the Center for Mind-Body Medicine, the Comprehensive Cancer Care III Conference in June 2000. The NCI presented two concurrent sessions at this conference discussing how to perform a best case series and opportunities for funding of CAM cancer research.

In June 2000 OCCAM launched a web site (http://occam.nci.nih.gov) to communicate better with the general public, research, and practice communities. The site contains descriptions of current and planned NCI CAM projects, serves to project a visible research agenda and to make more transparent NCI's processes for handling CAM issues (e.g. The Best Case Series Program).

The NCI, through the OCCAM and the Office of Cancer Communication, and with the assistance of the NCCAM, is developing summaries of the literature about various CAM modalities. These summaries are available on the CancerNet website (http://cancernet.nci.nih.gov) or from the Cancer Information Service (1-800-4CANCER). Five such summaries were developed in FY 2000 and new summaries will be completed and fully reviewed quarterly.

The NCI continues to be involved in several other projects related to complementary and alternative medicine. Two preliminary studies (one Phase I and one Phase II) of the activity of components of green tea were initiated in FY 2000. The Phase I study has been completed and a follow-up study is planned to begin in the next few months. The Phase II study should be completed soon.

The NCI is also supporting intramural research in CAM and cancer. The preliminary results of a survey of the use of alternative medical therapies in adult cancer patients enrolled in Phase I clinical trials were presented as a poster both at the annual meetings of the American Society of Clinical Oncology and the Oncology Nursing Society and found that 35 percent of patients on these trials were also taking CAM therapies.

Also, a clinical trial of the potential therapeutic role of a soya compound (genistein) in cancer patients

was recently completed and the data is being analyzed. The study examined the plasma concentrations of isoflavones induced by a single dose of two different preparations of oral genistein extracts. The investigators saw no drug related toxicity. A multidose, follow-up trial is planned.

A priority for the coming year is the development of an NCI CAM Clinical Trials Program. This program would initiate a process for developing and implementing a prospective agenda for important and definitive CAM cancer clinical trials. Potential CAM modalities would be selected on the basis of hypothesis generating studies (epidemiologic studies, observational studies, retrospective reviews or best case series), reviews of current literature about various CAM modalities, and the degree of use among the U.S. population.

The NCI will work with the NCCAM to amplify the existing CAM Citation Index which contains information about thousands of scientific articles about the use of CAM in various medical conditions. This database will include articles and abstracts from many databases including Medline or Web of Science and will be a resource for both the general public and researchers. This archive will also facilitate the production of systematic reviews of CAM cancer literature to inform the NCI's prospective research agenda.

The NCI intends to work with the NCCAM and the CAM and conventional research and practitioner communities to identify important and promising CAM approaches to cancer management and to facilitate their scientific evaluation. We will increase access of CAM practices to the processes of scientific review and evaluation at the NCI and NIH. This will be accomplished by the OCCAM providing assistance to direct the referral of these individuals to the appropriate groups within the NIH.

Item

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 NCI to continue its support of research in this area. In addition, the Committee has included sufficient funds for NCI, through a contract it has developed with CDC, to implement a national education program for consumers and health professionals. The Committee expects NCI and these other agencies to continue to consult with organizations representing individuals impacted by DES as they carry out DES research and education efforts. (p. 117)

Action taken or to be taken

Please refer to pages NCI-48 through NCI-49 of this document for NCI’s response to this significant item regarding DES.

Item

Esophageal and stomach cancer -- . . . . The Committee urges the National Cancer Institute in conjunction with the National Institute of Diabetes, Digestive and Kidney Disorders to augment its efforts in these areas, and to focus resources on the genetic aspects of these cancers; diagnostic tests for genetic abnormalities and prevention efforts; the modulation and understanding of epithelial injury and repair; environmental factors; and the development and treatment of Barrett's syndrome in patients with gastroesophageal reflex disease. (p. 117)

Action taken or to be taken

Please refer to pages NCI-50 through NCI-51 of this document, for NCI's response to this significant item regarding Esophageal and Stomach Cancer.

Item

Head and neck cancer -- It has been brought to the Committee's attention that there is a need to develop molecular markers that are predictive of the presence or likelihood of regional metastasis in patients with head and neck cancer. Such molecular markers would not only provide useful prognostic information but would identify patients at risk who could benefit from early elective treatment of the regional lymph nodes. The Institute is urged to expand its research support in this important area. (p. 117-118)

Action taken or to be taken

Please refer to pages NCI-59 through NCI-61 of this document, under Molecular Markers, for NCI's response to this significant item regarding Head and Neck Cancer.

Item

Hepatocellular carcinoma -- It has been brought to the Committee's attention that there is a need to determine the mechanism and the natural history of the development of hepatocellular carcinoma in patients with hepatitis C. The Committee encourages the Institute to develop a comprehensive research portfolio in this area and looks forward to learning of the progress made in this area prior to next year's hearing. (p. 118)

Action taken or to be taken

Based on recent data, liver cancer is the 7th most common cancer worldwide, with an estimated 427,000 new cases diagnosed annually (5.4 percent of all new cancer cases). It ranks fourth in terms of mortality, behind lung, stomach and colon cancers. Over 90 percent of primary carcinomas of the liver are hepatocellular carcinoma (HCC). Recent studies indicate that the incidence of HCC in the United States is rising, while the rates of most other cancers are declining. These trends further emphasize the need for the continued study of liver cancer. Many scientists think that this increase is the result of an increased prevalence of chronic infection with the hepatitis C virus (HCV), which occurs

in 60-80 percent of those infected. Infections with HCV are frequently unrecognized by patients because the initial symptoms are quite mild. When the infection is detected, often years later, significant liver damage, sometimes including cancer, has ensued. Thus, studies of this agent are important not only because it is highly infectious, but because the long-term consequences of such infections include both liver damage severe enough to require liver transplantation as well as liver cancer. The viral-chemical etiology and molecular mechanisms of pathogenesis of these diseases remain largely unknown.

Before significant progress can be made in studies of HCV, several important roadblocks need to be overcome. Among the tools that scientists need are the development of suitable in vitro (test tube) and animal model systems, identification of parts of the virus that could result in protective immunity as well as some means to test their efficacy and effectiveness, and methods of characterization of protective versus immune tolerance host responses to viral infection.

The NCI is supporting studies on the mechanism(s) and natural history of the development of hepatocellular carcinoma associated with HCV infection by extramural investigators at colleges and universities, and also by intramural NCI scientists in Bethesda. The Institute is also participating in the NIH hepatitis C virus working group, a coordinating body with representatives from all of the NIH Institutes and Centers with interests in HCV.

Several NCI-funded extramural investigators have been working on establishing fundamental properties of HCV and attempting to produce suitable in vitro model systems to study the virus. One of these investigators has worked on the establishment of cell culture models to replicate HCV in liver and lymphoid cells by full-length HCV RNA transfection and has compared these results to those found in human livers infected with HCV, and in liver cancers. He determined that the level of HCV replication in the RNA transfected cell culture is comparable to that seen in the body (*in vivo*) during HCV replication. The two HCV cell culture systems in hepatic and lymphoid cells will serve as model systems to address many important questions that are relevant to hepatitis C virus infection in humans. In addition, the HCV RNA transfected cultures were shown to be infectious to chimpanzees. Using this infectious clone, an inducible model of HCV infection was established to study its replication. The investigator is also attempting to determine if HCV replication in cell culture systems can be inhibited using several basic approaches. Preliminary findings suggest that an adenovirus carrying antibodies to HCV proteins may be a good candidate to inhibit hepatitis C virus production. If substantiated, this observation could provide the basis for a possible anti-viral strategy against HCV infection.

Another extramural investigator is studying the response of the human host to HCV infection. In this study, special techniques were used to separate and characterize the responses of particular types of immune cells, the helper T-lymphocytes ($CD4^+$) and the cytotoxic/suppressor T-lymphocytes ($CD8^+$) in patients. The results showed that the HCV-specific $CD4^+$ T cell response is stronger in individuals recovering from infection than in chronically infected individuals and that this response is maintained indefinitely after viral clearance, whereas HCV specific $CD8^+$ CTL activity is higher during chronic infection than after viral clearance. HCV specific $CD8^+$ T cells were only rarely detectable without several weeks of viral antigen stimulation. In addition, after growing them outside the body, $CD8^+$ T cell lines from chronically infected patients were less likely to produce gamma interferon (IFNã), a

substance produced by the body in response to viral infection that is important in elimination of the virus, than those derived from recovering individuals. These results suggest that the $CD4^+$ T cell response is more closely associated with HCV clearance than the $CD8^+$ T cell response, which is more often associated with viral persistence and chronic liver disease perhaps because its cytolytic activity is not balanced by its ability to produce IFNã in these patients.

Another study, initiated by this same investigator defined the characteristics of the antiviral T cell response during the early stages of infection. To accomplish this goal, the T-cell response to HCV was studied in 13 health care workers who experienced documented high risk needle stick exposures to HCV. All exposures involved hollow bore needles, and all induced bleeding in the exposed individual. The exposed health care workers were followed for anti-HCV seroconversion and for the presence of virus in the blood by sensitive tests for up to 6 months after exposure. Peripheral blood proliferative T-cell responses to 4 HCV proteins were also monitored. Neither HCV viremia nor antibody serconversion occurred in 11 of the 13 patients, and none of them developed significant HCV-specific T-cell responses at any time in the follow-up period. In contrast, two of the patients who seroconverted and became HCV RNA positive displayed strong proliferative T cell responses to all 4 HCV proteins beginning between 4-8 weeks after exposure. These responses corresponded with anti-HCV serconversion and with the clinical onset of viral hepatitis. Despite these T cell responses, both of these patients became persistently infected. These results show that needle stick exposure to HCV does not prime a T cell response in the absence of seroconversion and the appearance of HCV RNA. This implies that infection, not merely exposure, is needed in order to induce an immune response to this virus. The results also demonstrate that a T-cell response to HCV is a relatively early event during HCV infection, that it coincides with the appearance of antibodies and liver enzyme elevations and that it does not lead to viral clearance in these individuals. Further clarification of the role of the T-cell response in the outcome of HCV infection will require a large-scale, prospective, quantitative and qualitative analysis of the $CD4^+$ and $CD8^+$ T-cell response in many patients who ultimately either clear of the virus or become chronically infected.

Taken together, the results of these studies demonstrate that HCV can establish an infection and persist indefinitely in the face of a vigorous T-cell response, which is a relatively rare event during infection. The data also suggest that the $CD4^+$ T-cell response may play a greater role in viral clearance than the $CD8^+$ T-cell response which is probably responsible for the liver disease that the virus initiates. These results suggest that it may be difficult to develop vaccines and immunotherapeutic strategies for the prevention and treatment of HCV infection. Clearly, the immunological pathways able to control the infection, and the mechanisms used by the virus to evade those pathways must be defined before these goals will be achieved. The availability of transgenic mice that express the HCV core protein in a completely controllable fashion now makes it possible to examine the functions of that protein that could contribute to immune evasion. They also support planned experiments to define the early events in immune recognition of HCV and the capacity of the virus to suppress those events.

A significant problem in studies of HCV-induced disease is that the only available animal model for the disease is the chimpanzee, a protected species. Another NCI-funded investigator has continued to follow two chronically infected animals as well as a chimpanzee who resolved the infection. Shifts in the

HCV nucleic acid sequence have been found, with several changes not common between the two animals, that appeared shortly after the acute phase. In the animal that resolved the infection, rechallenges with chimp titered acute phase homologous virus obtained from one of the chronically infected animals have been undertaken. Remarkably, this animal was reinfected at the same dose as a naive control animal but again resolved the infection with lower viremia and little evidence of liver injury. Higher doses of an identical virus were sometimes able to establish productive infection (as measured by detectable viremia) but in some cases sterilizing immunity was obtained. The investigator will be continuing these studies focusing on the immune response correlates of resolution versus chronic infection.

Studies have also been carried out using a live attenuated bacterium that carries a protein fragment of the hepatitis C virus. Preliminary studies in mice given the bacteria by mouth demonstrated that 21 of 23 mice (91 percent) that received the standard dose displayed significant cytotoxic T-lymphocyte (CTL) responses against the peptide, which was previously shown to be found in humans who had recovered from hepatitis C. The minimal amount of DNA required to induce HCV specific CTLs was at least 10,000 times lower than with conventional intramuscular DNA immunizations, demonstrating that the oral dosing was much more effective. *In vivo* protection lasted for at least 4 months after immunization. Since oral immunization with live, attenuated bacteria as a carrier for HCV-DNA is a potent strategy to induce long-lasting HCV specific CTL responses in mice, these investigators will further test this immunization strategy in chronically HCV infected chimpanzees and monitor its effects on amount of virus, liver enzymes and peripheral blood intrahepatic cellular immune responses.

Another extramural scientist has conducted inhibitor experiments to determine if currently used standard therapies active against HCV have direct effects on HCV RNA replication. He has found that HCV RNA and protein synthesis are selectively inhibited by interferon alfa, the only clinically effective single therapy against HCV infection. However, HCV RNA replication is not inhibited by ribavirin, which is active against HCV when administered in combination with interferon but not alone. These findings demonstrate that interferon, in addition to its immunomodulatory actions, has direct antiviral effects on HCV infection, and that ribavirin is acting indirectly to control HCV infection when given in combination with interferon.

Several extramural epidemiologists are carrying out ongoing cohort studies. The aim of the first is to follow-up Chinese, Senegalese and Philadelphia-Asian American cohorts to identify factors that may account for the variation in risk of hepatocellular carcinoma among the study participants. The second cohort study seeks to understand HTLV-I and hepatitis C co-infection in relation to virus-associated disease, and to understand the role of the host immune response, and the effect of dual infection on risk for development of HCV.

Two new epidemiologic studies were recently funded in response to one of the collaborative RFAs mentioned above. The broad, long-term objective of the first study being conducted at St. Jude Children's Hospital is to prospectively follow a well-defined cohort of survivors of childhood cancer who were inadvertently infected with hepatitis C by transfusion with HCV contaminated blood during medical treatment in order to develop predictive models for the subsequent development of cirrhosis,

chronic active hepatitis, fibrosis, hepatoma, hepatocellular carcinoma and other HCV-related hepatic sequelae. The aim of the second cohort study is to conduct a molecular epidemiologic investigation to examine the interrelationships among viral, genetic and environmental risk factors for hepatocellular carcinoma among residents of Egypt, which may have the world's highest prevalence of this disease because of use of contaminated needles in medical procedures many years ago.

An NCI intramural scientist is investigating the hypothesis that the HCV core antigen is involved in causing liver cancer. This may occur through at least two activities of the viral core, in decreasing the activity of cellular anti-viral substances and also by inducing genetic instability in the infected liver cells. Further experiments are underway to determine if either or both of these mechanisms are involved in causing HCV-associated human liver cancer. The investigator is characterizing changes in gene expression during the genesis of HCC, which currently are largely unknown. Efforts to identify gene expression profiles will contribute to the establishment of novel markers with potential diagnostic and prognostic value for HCC, and analysis of these genes would provide further understanding of the genesis of liver cancer and provide further insights into designing strategies for HCC-directed molecular therapy. Using both DNA array technology and serial analysis of gene expression, he is searching for novel genes and identifying common changes in gene expression during viral hepatitis-mediated liver cancer. By comparing liver samples from normal, precancerous and HCC patients, these approaches allow him to identify candidate genes whose expression are associated with HBV or HCV-associated HCC. He plans to determine molecular profiles during the progression from primary tumors to metastatic lesions of HCC. Work will continue to explore these genes that may contribute to the establishment of markers with potential diagnostic and prognostic value for HCC, which can also be used as potential targets for molecular therapy.

Other NCI intramural investigators will conduct epidemiological studies focused on the causes of hepatocellular carcinoma in the U.S. Population during the 1990s, with special emphasis on the role of HCV in these tumors. A representative sample of tumor tissue from patients with hepatocellular carcinoma that was collected by NCI's SEER registries will be examined for molecular evidence of HCV and hepatitis B virus (HBV). The investigators will also examine the possible role of hemochromatosis genes and other host gene differences in the development of this cancer. This collaborative study includes investigators from the NCI and the Armed Forces Institute of Pathology.

The rates of infection with HCV have been followed since 1982 in a cohort of more than 2,000 persons with hemophilia in the Multicenter Hemophilia Cohort Study. This study is underwent a major expansion in 2000 (MHCS-II) that greatly increased the number of HCV-infected patients in the cohort. The incidence of hepatocellular carcinoma and potential contributing factors in the etiology of this cancer will be examined.

Other NCI intramural investigators are collaborating on a NIDDK sponsored randomized trial of the effect of long-term treatment of HCV infection with interferon treated with a chemical called polyethylene glycol, which seems to enhance the antiviral activity of interferon. The subjects are HCV-infected patients with advanced liver disease who are at high risk of developing hepatocellular

carcinoma. This prospective study offers an opportunity to further examine, in this population of patients, how infection with HCV can lead to the development of hepatocellular carcinoma.

Finally, other NCI intramural investigators, in collaboration with researchers in the United States, Egypt, and the Peoples' Republic of China, are pursuing a genetic study of host factors that are involved in HBV and HCV viral clearance, liver inflammation, and the development of HCC. The high incidence of hepatocellular carcinoma and HCV infection in these countries make them ideal for such studies. The investigators have an inventory of over a thousand cell lines from Asians, African Americans, and U.S. Caucasians to study candidate genes involved the pathway from HBV/HCV infection to liver cancer.

As previously mentioned, NCI is actively involved in the NIH hepatitis C virus working group. This group was mentioned in Congressional appropriations report language in 1997 which requested that the NIH form a working group whose charge would be to develop an integrated NIH-wide plan for hepatitis C. The Inter-Institute Hepatitis C Virus Working Group began in November 1997 and operates primarily via the extramural research programs of the NIH. Meetings have generally been held biweekly or monthly, with representation from the NIAID, NCI, NIDDK, NIAAA, NIDA, NHLBI and the NCRR, along with the National Center for Complementary and Alternative Medicine (NCCAM), the NIH Center for Scientific Review, and the National Center for Minority Health and Health Disparities (NCMHD).

The Working Group's functions are to share information about current activities in order to develop collaborations based on existing common interests and to accomplish institute objectives more quickly through existing resources; foster the development of individual institute research agendas; develop a document that incorporates these research agendas into an overall NIH agenda that defines important research areas and the research resources needed to address them; focus attention on specific areas through meetings and workshops; and develop new initiatives that address this agenda and encourage participation of multiple NIH institutes as appropriate.

NCI continues to contribute significantly to these goals. Institute staff had a significant role in the development of the NIH HCV Framework for Progress, which has been approved by the relevant IC Directors and is currently in final review at NIH. In addition, the Institute has contributed both time and dollars to a multi-Institute sponsored request for grant applications to study pathogenesis, natural history, therapy and prevention of HCV infection and associated liver damage, including cancer. This initiative resulted in significant new research activity in HCV-associated diseases. NCI also cosponsored two NIAID RFAs utilizing the Small Business Innovative Research mechanism. These targeted efforts seek to encourage small businesses to participate in the development of small animal models to study acute and persistent HCV infection, fibrosis/cirrhosis, and liver tumor development. The potential business application of such models is preclinical development and evaluation of both antivirals and vaccines.

A workshop, on "Hepatitis C in African-Americans" organized by NIDDK along with NIDA, NIAID and the NCMHD was held in December 1999. Recent studies suggest that African-Americans have a higher incidence of hepatitis C compared to other racial and ethnic groups in the United States; and that

the disease course, outcome and response to interferon therapy may be worse in African-Americans than in the Caucasian population. Focusing on possible causes for these disparities, the workshop identified potential research strategies for therapy and prevention of this disease in this population, which are also addressed by the NIH Hepatitis C Framework for Progress.

Thus, the NCI continues to be actively involved in support of studies of the viral etiology and epidemiology of hepatocellular carcinoma by extramural and intramural scientists. NCI also maintains an active role in the NIH hepatitis C working group. Through its interactions with other participating NIH institutes, NCI has co-sponsored a number of research activities and conferences that contribute significantly to our knowledge of HCV. These cooperative activities developed a research program that maximizes return on research funding by cooperative interaction with other NIH institutes and co-funding research activities of mutual interest to address important overarching scientific issues beyond the scope of any one institute.

Item

Imaging systems technologies -- . . . . The Committee continues to support NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee continues to encourage the large scale testing of women for breast cancer and of men for prostate cancer to demonstrate and quantity the increased diagnostic and staging capabilities of PET relative to conventional diagnostic and staging technologies including mammography. (p. 118)

Action taken or to be taken

As recently as 25 years ago, a physician or surgeon who suspected the presence of a tumor in a patient had few options. They could only order x-ray studies to define and localize the tumor as accurately as the pictures would permit and/or schedule the patient for surgery and examine the tumor directly, excise a portion of the unhealthy tissue for biopsy, remove the tumor if possible, and explore surrounding tissues to determine whether the cancer had spread.

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

NCI-Industry Forum and Council

In September 1999, NCI held the first National Forum to bring together representatives of the imaging industry, academics, NCI, FDA and HCFA. Over 250 participants attended the 1-day public meeting. On the following day, a workshop addressed many of the issues raised in the Forum. Proceedings detailing the suggested actions were circulated and verified. One important issue was to provide a means for industry to get advice on how to better collect the information needed to meet regulatory and reimbursement requirements while evaluating the scientific merit of the new technology. The written reviews of the forum were excellent. There was considerable positive feedback from all parties about the value of such meetings to facilitate the processes involved in getting potential products related to imaging of oncology through the necessary testing and approval activities and into the marketplace. The Second National Forum was held on September 14-15, 2000.

In addition, the First Forum led to a series of monthly conference calls that included representatives of all the parties to continue communications about issues related to imaging probes and devices. Another activity that grew out of these discussions at the First Forum and the follow-up conference calls was the formation of the NCI-Industry Council. This council provides a means for individuals or companies with an idea or proposed products to present their questions in a confidential meeting, to all three relevant government agencies, i.e., NCI, FDA, and HCFA. A request for questions to the Council was publicly issued in May 2000, and 18 responses were received. Three of these were selected for the initial Council meeting held in July 2000. The companies received verbal input from members of the council at the meeting, followed by a written critique. The critique was non-binding to the agencies, but represented a high level analysis to help the industrial representatives proceed with further evaluation of their new technologies. Responses from the three participants who presented to the Council were very positive. Future Council meetings will be held quarterly. NCI is optimistic that these ongoing Forum and Council meetings will foster improved cooperation and collaboration among all parties, which will in turn lead to making new imaging products available as quickly as possible within the framework of assuring safety and efficacy.

PET-related Research Activities

Malignant tumor cells have a high rate of glucose utilization (glycolysis), and there is an associated increased capability for transferring glucose, or glucose-like compounds such as FDG, across the tumor cell membrane. (F-18) fluorodeoxyglucose (FDG) has proven useful for tracing glucose metabolism, for detecting malignant tissue and for quantifying changes in tumor glycolysis during and after treatment. Clinical applications using FDG-PET have been introduced for diagnosis, staging and monitoring therapy of various cancers in the past 5 years. Compounds other than fluorodeoxyglucose, such as amino acids, labeled with positron emitters are also potentially useful for PET scanning, and a variety of NCI programs, described below, facilitate that research.

NCI has steadily increased its support for PET scanning from 29 projects in FY 1998 to 81 funded studies in FY 2000. Sixteen of the 81 are clinical studies involving patient imaging. The patient studies involve a variety of cancers including brain, breast, and colon cancer, childhood adrenal cancers, soft-tissue sarcomas, and melanoma. Four of the 81 are pre-clinical centers involving PET imaging of small animals. Eighteen are related to further development of PET related technology. Thirty-one are PET-

related basic science research. Included in the PET-related research activities is the recent initiatives of Molecular and Cellular Imaging Centers (ICMIC) and the Planning Grants for Molecular and Cellular Imaging Centers (pre-ICMIC). PET is expected to be a critical and important imaging technique used in these particular centers. In the three currently funded ICMIC grants there is a great deal of innovative PET research being proposed. The proposal from one ICMIC has five projects, all using micro-PET imaging, to investigate various cancer-related topics. The proposal from another ICMIC has three projects related to conventional PET and micro-PET imaging in exploring imaging of gene expression, the use of FDG-PET to better characterize prostate cancer, and development of new PET radio-tracers to examine proliferative activity of tumors. The proposal from a third ICMIC will also begin to use various PET techniques to explore cancer cell signaling abnormalities. In the ten funded pre-ICMIC proposals, PET is an important and integral part of more than half of the projects proposed to study the molecular basis of cancer.

RFAs for both the Molecular and Cellular Imaging Centers (ICMIC) and the Planning Grants for Molecular and Cellular Imaging Centers (pre-ICMIC) have been reissued for FY 2001 awards. It is expected, as in the first set of applications for both of these programs, that PET will be an important and integral aspect of the research plans. We plan to award six additional pre-ICMIC grants and two ICMIC grants in fiscal year 2001. Two additional ICMIC grants will again be awarded in fiscal years 2003 and 2004. This will then make a total of nine ICMIC awards and 16 pre- ICMIC awards by the completion of these major initiatives in fiscal year 2009.

Clinical Trials Using PET

The NCI-funded diagnostic imaging cooperative group, American College or Radiology Imaging Network (ACRIN), has begun a study in collaboration with the Southwest Oncology Group (SWOG) to look at the ability of FDG-PET to predict response to therapy in patients with lung cancer. ACRIN is also planning a cooperative study with SWOG to study the use of FDG-PET in staging melanoma. Both of these studies will be multi-institutional and will accrue about 200 patients each.

The NCI-funded cooperative group, American College of Surgeons Oncology Group (ACOSOG), is currently running two clinical trials that will assess the use of FDG-PET as an alternative to surgical staging. One of the trials will study patients with lung cancer, and the other will study patients with esophageal cancer. Both studies are multi-institutional.

Research to Develop New PET Agents

The NCI has funded several initiatives to support discovery, development and validation of target-based therapy, many of which will have an impact on PET-related research. Pre-clinical and clinical research with novel agents for cancer treatment and prevention require tools such as PET imaging to determine that the agent has affected the intended molecular target. The ability of in-vivo PET imaging to convey information about the molecular pathways and endpoints of these therapeutic agents is extremely important. There are an increasing number of potentially useful PET imaging agents under development

in research laboratories throughout the country which will have the capability to image these important biological processes.

$ NCI will provide support for continued laboratory development of molecularly-targeted imaging agents. The newly proposed Development of Clinical Imaging Drugs and Enhancers (DCIDE) program will facilitate some of the work necessary to bring agents to the point of IND approval. The DCIDE program is intended to supply critical missing steps in the development and validation of imaging compounds, including PET agents. The DCIDE program will focus on promising imaging agents including many PET labeled compounds that are not otherwise likely to receive an adequate and timely evaluation.

$ Improvement in the PET scanning technology is also taking place. The new NCI Program Announcement for R21/R33 Phased Innovation Awards for imaging technology will assist with this technology development.

$ These promising new PET agents and technologies will have to be tested in Phase I, II and III clinical trials. A proposal to fund the Phase I and II imaging trials (Safety and Preliminary Clinical Efficacy) has been approved and will begin in 2001. ACRIN and other NCI-funded Cooperative Groups provide a mechanism for Phase III trials of potentially important PET studies.

Digital Mammography and Application of Imaging Technologies to Breast Cancer

Please refer to pages NCI-40 through NCI-44 of this document for NCI's response regarding digital mammography and application of imaging technologies to breast cancer.

Imaging Systems Technologies

Status of Selected Ongoing Programs - Program Announcements

$ Innovative Technologies for the Molecular Analysis of Cancer: Phased Innovation and Small Business Awards and Applications of Innovative Technologies for the Molecular Analysis of Cancer: Phased Technology Application and Small Business Awards: This series of 4 PAs focuses on the development and application of molecular analysis technologies in studies relevant to cancer research. Molecular analysis technologies of interest include those that are entirely novel, or emerging but not currently in broad scale use, or technologies currently in use for one application or set of applications, that are being evaluated for utility for alternative applications. Imaging research, including chemistries, hardware and computational tools to support imaging of molecular species in cells or whole organisms, can be supported under this program. Currently one imaging project is funded through this mechanism.

$ Bioengineering Research Grants (BRGs) and Bioengineering Research Partnerships (BRPs): These are joint initiatives from many Institutes and Centers of the National Institutes of Health

(NIH) to support basic bioengineering research whose outcomes are likely to advance health or health-related research. Bioengineering integrates principles from diverse fields, and the creativity of interdisciplinary teams is resulting in new basic understanding, novel products and innovative technologies. Bioengineering also crosses the boundaries of academia, science, medicine, and industry. These projects are often focused on technology development rather than on proving or disproving a scientific hypothesis, and therefore, the NIH review criteria for bioengineering proposals in response to these PAs have been modified to ensure that these proposals are evaluated appropriately and fairly. Applications are encouraged from individual investigators (BRGs) or multidisciplinary groups of investigators (BRPs). Although not limited to imaging research, many applications for both BRGs and BRPs have been submitted by the imaging community. In the first round of BRP applications, one imaging application was funded and one was co-funded with another institute. In the next round, 13 imaging applications were received; as many as four of these will be funded in FY 2001.

Cooperative Trials in Diagnostic Imaging: ACRIN is an NCI-sponsored Cooperative Group that was established in December 1998 to perform multi-institutional clinical trials in diagnostic imaging related to cancer in a timely and flexible manner. As a national clinical trial resource, ACRIN provides a stable infrastructure within which to conduct clinical trials. If investigators have an idea for a large-scale clinical trial, but do not have access to sufficient numbers of clinical patients to adequately implement such a trial, ACRIN resources are competitively available. Examples of clinical trials that ACRIN is focusing on are:

- **$** Role of Radiology in the Pretreatment Evaluation of Invasive Cervical Cancer: Compare clinical Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging to pretreatment evaluation by CT and MRI in cervical cancer.

- **$** Positron Emission Tomography (PET) Imaging of Lung Cancer Response to Therapy: This trial will use FDG PET to monitor the changes due to chemotherapy. Since all patients will have surgery after the last PET scan, a direct comparison of imaging and pathological results is possible.

- **$** Computerized Tomographic Colonography: Performance Evaluation in a Multicenter Setting - This study examines the accuracy of computerized tomography colonography (CTC) as a potential new tool for colon cancer screening. CTC, sometimes called virtual colonoscopy, uses virtual reality technology to produce two- and three-dimensional images of the entire colon, thus permitting thorough evaluation without the invasiveness of traditional colonoscopy procedures.

- **$** Digital versus Screen-Film Mammography

- **$** Contemporary Screening for the Detection of Lung Cancer Pre-Malignancy and Malignancy - This project is a multicenter, randomized controlled trial of 7,000

individuals at high risk of lung cancer to address whether screening using low-dose helical CT can improve lung-cancer specific mortality.

Diagnostic Imaging and Guided Therapy in Prostate Cancer Grants and Small Business Grants: This initiative was designed to encourage research on improved imaging methods for image-guided biopsy or therapy of prostate cancer. The specific goals included the development and application of one or more of the following inter-related components: (a) means for measuring local extent of disease using anatomic, metabolic or alternative novel imaging methods, (b) means for improved image-guided biopsy, staging or identification of aggressive cancers by metabolic or alternative novel imaging methods, and (c) means for navigation and control of image-guided therapy or measurement of early biological effects of therapy. Forty-one applications were received from institutions and corporations and 23 from small businesses. Of these, 12 will be funded by the NCI and another three by the NIA which participated in the RFA; five of the SBIRs will be funded.

Image Database Resource for Image Processing Research: Image processing algorithms are increasingly important, as biomedical imaging becomes more electronic in terms of image acquisition and display. However, the development of optimal image processing software has been hampered by the lack of standardized sets of data upon which to test new algorithms and display the results. This RFA, issued in April 2000, with applications received in July 2000, will support a consortium of institutions to develop the necessary consensus and standards for a lung CT image database resource, and to construct a database of spiral CT lung images. This initiative will essentially serve as a "demonstration project", to demonstrate that a group of experts focusing on just one organ system and one modality can develop a process that will serve as a model for other groups to develop additional image database resources. Fifteen applications have been received; it is expected that five institutions will be funded.

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

Ultrasound Research Interface: Clinical ultrasound procedures currently comprise a significant fraction of imaging studies in the United States, and ultrasound is a leading modality in terms of its clinical impact. The manufacturers restrict investigator access to the electronic signals inherent in ultrasound. In ultrasound medical imaging, radio frequency pulses stimulate a transducer probe to generate ultrasound waves. The detected echoes reflected from different biologic structures form images. However, access to raw unprocessed echo data is not possible in commercially available ultrasound machines as it is in MR or CT. This is a significant impediment to research on new ultrasound techniques by biomedical engineers. Manufacturers' reluctance in providing access to the echo data has been based on cost, proprietary issues, safety, and liability considerations. An ultrasound interface is necessary as a research resource to overcome this barrier. Ultrasound manufacturers have agreed that proprietary, safety, and liability issues can all be addressed.

The intent of this RFP is to develop powerful ultrasound research interfaces that allow extensive control over a wide range of system parameters. These interfaces will be software add-ons to continuously evolving scanner control software. Although the creation of these interfaces relies on access to proprietary information, protective software shells can restrict such access while still allowing access to control parameters. This RFP will allow research interfaces to be developed by several leading ultrasound manufacturers to maximize the research impact for the ultrasound imaging community. The operational characteristics required by this contract will allow the user to: (a) find targets of interest using conventional (commercially-available) B-mode and Doppler methods, (b) enter into a "research mode" with user-programmed scanner parameters, and (c) store raw echo signals during operation in the research mode.

Item

Lymphoma -- The Committee is pleased that the NCI is committed to conducting a progress review group (PRG) on lymphoma. The PRG on lymphoma will afford NCI and other Federal agencies the opportunity to evaluate current research and determine future needs in lymphoma research. The Committee requests that NCI be prepared to report to the Committee at the fiscal 2002 hearings on the progress of the PRG on lymphoma and the development of a prioritized national research agenda for lymphoma. (p. 118)

Action taken or to be taken

Please refer to pages NCI-52 through NCI-58 of this document for NCI's response to this significant item regarding Lymphoma.

Item

Multiple myeloma -- The Committee is pleased that MM was included in an NCI Progress Review Group and looks forward to hearing about the Institute's plans for the PRG findings at next year's hearing. The Committee continues to strongly urge support to address epidemiological and other data gathering activities relevant to MM and coordinate efforts with the Centers for Disease Control and Prevention, the Office of Rare Diseases, the Office of Research and Minority Health, and NIEHS. (p. 118-119)

Action taken or to be taken

Please refer to pages NCI-62 through NCI-65 of this document for NCI's response to this significant item regarding Multiple Myeloma.

Item

Multiple myeloma -- The Committee encourages the Institute to disseminate information and educate the public and health professionals about the symptoms of and treatment for MM. (p. 119)

Action taken or to be taken

Please refer to pages NCI-62 through NCI-65 of this document for NCI's response to this significant item regarding Multiple Myeloma.

Item

Neurofibromatosis (NF) -- The Committee encourages NCI to strengthen its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation and clinical trials. The Committee also urges NCI to continue to coordinate its efforts with other Institutes engaged in NF research and be prepared to report on the status of the NF research portfolio at its fiscal year 2002 appropriations hearing. (p. 119)

Action taken or to be taken

Please refer to pages NCI-67 through NCI-69 of this document for NCI's response to this significant item regarding Neurofibromatosis.

Item

Nutrition Therapy -- . . . . The Committee encourages the Institute to conduct research to assess changes in patient quality of life as a result of nutrition intervention. The committee further encourages the Institute to conduct randomized clinical trials of older cancer patients are necessary to determine whether a relationship exists between nutrition support and clinical outcomes for cancer patients. (p. 119)

Action taken or to be taken

NCI plans to support a broad range of research initiatives in areas of intervention, behavioral science and communications as related to using nutrition and nutritional initiatives to reduce cancer risk and possibly improve outcomes. For instance, evidence from ecological, epidemiological, and laboratory studies consistently supports the contention that diet may provide a protective effect against breast cancer and its recurrence. NCI is funding two major randomized controlled clinical trials - the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living Study (WHELS).

The WINS is testing the hypothesis that dietary fat intake reduction as an adjuvant to standard breast cancer therapy will reduce recurrence and increase survival for postmenopausal women (age 48-78 years) with localized breast cancer. This randomized controlled clinical trial is being conducted in 2,500 women (including approximately 16 percent minority women) enrolled at 38 clinical centers. Women

are randomized to one of two dietary groups: Intensive Intervention Group (IIG) or a control Non-Intensive Group (NIG). The IIG participants receive an individualized nutrition program targeted to reduce dietary fat intake to 15 percent of calories. The NIG participants receive information on the Dietary Guidelines for Americans which includes 30 percent of calories from fat and minimal ongoing nutrition education. Data is being collected on dietary intake, dietary supplement intake, food patterns, anthropometrics, and quality of life. Collection and banking of blood specimens will provide a unique resource for the future testing of hypotheses regarding mechanisms of dietary fat reduction.

The Women's Healthy Eating and Living Study (WHELS) is a multicenter randomized controlled trial testing whether a daily dietary pattern high in vegetables (5 servings), fruits (3 servings), 16 ounces vegetable juice, fiber (30 grams) and low fat (15-20 percent of calories) will affect the course of breast cancer in women (age 18-70 years) with Stage I, II, or IIIA disease after they have received standard treatment therapy. This trial is being conducted in 3,000 pre- and postmenopausal women enrolled at seven clinical centers. Women are randomized to one of two dietary groups: dietary intervention group (dietary counseling) or control group (no dietary counseling). Data collection includes dietary assessment, anthropometrics, health status and quality of life. Blood specimens are collected for measurements of carotenoids, lipds, estrogens, and future mechanistic studies of recurrence.

The results of these two dietary modification clinical trials will have major implications for future directions of research in breast cancer prevention and control of recurrence and provide insight into the mechanisms of how diet might influence this disease. These two clinical trials are expected to be completed in approximately 5 years.

Some of NCI's other nutrition-related activities include:
Collaborations on Nutritional Modulation of Genetic Pathways Leading to Cancer: NCI is developing a two-phase program for both basic and clinical research in areas related to dietary nutrients as modifiers of genetic pathways leading to cancer. The first RFA, recently released, invites applications for planning grants that will lead to collaborative interdisciplinary research teams to resolve complex gene-nutrient interrelationships that are related to cancer prevention. The second RFA, for Cooperative Specialized Centers, is expected to be released in FY 2002 and is meant to foster new interdisciplinary approaches to resolving issues about the physiological significance of dietary components as regulators of genetic and epigenetic pathways involved with cancer. It is expected that the information gained will provide guidance for the development of dietary intervention strategies that are effective in cancer prevention.

Diet, Lifestyle and Cancer in U.S. Special Populations: NCI has issued a program announcement for research applications that focus on epidemiologic studies to determine causes of cancer and means of prevention in African Americans, American Indians, Alaskan Natives, Asian and Pacific Islanders, Native Hawaiians, Hispanics, rural, older, low income and low-literacy groups. These groups experience unusually high incidence and/or mortality rates for some cancer sites. The reasons for the disparate rates may be differences in environmental exposures, socioeconomic factors, access and utilization of screening and treatment, the presence of inherited susceptibilities, and modifiable behavioral risk factors such as diet, weight, alcohol intake and physical activity.

In addition, NCI continues to support two Clinical Nutrition Research Units (CNRUs) with one located at the Sloan-Kettering Institute for Cancer Research in New York and the other at the University of California, Los Angeles (UCLA). The CNRU at Sloan-Kettering represents the central mechanism for coordinating the major efforts of its 5 participating institutions on nutrition, cancer prevention and control, and outreach. The CNRU at UCLA serves to integrate the research of the many academic units within UCLA and its 6 affiliated medical centers in genetics, cellular and molecular biology, and metabolism with clinical studies in nutrition and cancer prevention. The research supported by CNRUs are existing research projects funded through other mechanisms, and the purpose of the NCI-supported CNRUs is to provide shared resources that bring together investigators from relevant disciplines in a way that enhances and extends the effectiveness of research related to nutritional sciences and cancer prevention.

NCI's 5 A Day for Better Health Program is a national program that approaches Americans with a simple, positive message: eat 5 or more servings of vegetables and fruit daily for better health. In light of this objective, NCI and its award-winning 5 A Day program have supported extensive research in behavior interventions and communications to better understand the motivators and barriers to people eating more fruits and vegetables. Since the start of the 5 A Day program in 1991, further evidence has accumulated that supports the hypothesis that a diet rich in vegetables and fruit reduces the risk of cancer and other diseases. To improve the program, the Director of NCI established the 5 A Day Program Evaluation Group, composed of external experts in diet, weight and physical-activity research, to review and evaluate the program. The Evaluation Group recently released their comments which identified areas of research opportunities and made recommendations to the future direction of the program. NCI is evaluating the group's comments that, in general, stated that the program was effective but should be expanded to include collaborations with:

$ USDA: to better focus dietary guidelines and to promote research in agricultural and economic policies that encourage vegetables and fruit consumption.

$ Other NIH institutes: to promote research into the role of specific vegetables and fruits and their components in lowering disease; promote methodologic and applied behavioral research; expand the awareness of the scope of chronic and deficiency diseases that may benefit from increased consumption of vegetables and fruit; and develop a comprehensive surveillance plan to monitor vegetable and fruit consumption and the psychosocial and economic factors related to it.

$ CDC: to develop and manage state-level 5-A-Day programs.

Item

Ovarian and cervical cancer -- . . . . The Committee strongly urges NCI to expedite current research on screening methods to detect, diagnose, and identify staging of ovarian cancer. The Committee encourages the Director of the NCI to fully fund the four ovarian cancer SPOREs in fiscal

year 2001 and potentially issue a new request for applications for additional ovarian cancer SPOREs. The Committee also believes that identification of a cost-effective screening strategy could result in earlier diagnosis for women and higher cure rates. Similarly, 15,000 cases of cervical cancer are diagnosed annually, and 5,000 women die from the disease. NCI is strongly urged to accelerate research in this area. (p. 119)

Action taken or to be taken

NCI is committed to improving the prevention, detection, and treatment of ovarian and cervical cancers. All four ovarian cancer Special Programs of Research Excellence (SPOREs) will be fully funded in FY 2001, and NCI expects these new ovarian cancer SPOREs – which support innovative, multidisciplinary research with the potential to have an immediate impact on cancer care and prevention – will be important hubs of progress against this disease. The SPORE program will be substantially expanded between FY 2001 to FY 2003 to add seven new cancer sites including a gynecological (endometrial/cervical) cancer solicitation in FY 2003. In addition, another ovarian SPORE solicitation will be issued in FY 2003.

Also, in early FY 2001, NCI established a Progress Review Group (PRG) to assist in setting long-term priorities for research on gynocological cancers, including ovarian and cervical cancers. Like other PRGs, this one will be composed of between 20 and 30 prominent members of the scientific, medical, industry, and advocacy communities who are charged with outlining and prioritizing a national research agenda for a particular cancer site. Using the NCI's current research program as a baseline, the PRG will identify priority areas for research and will issue a final report listing research priorities and resource needs. This report is scheduled for completion by the end of FY 2001 and NCI will develop an implementation plan by mid FY 2002.

Item

Pancreatic cancer -- The Committee is concerned that pancreatic cancer, the fourth leading cause of cancer deaths for men and women in the United States, is projected to claim the lives of nearly 30,000 Americans this year alone. The 5-year survival rate for pancreatic cancer, 4 percent, is the lowest of all cancers. The Committee is concerned that pancreatic cancer is not diagnosed until advanced stages when treatment options are limited and largely ineffective. The Committee expects the NCI to be prepared to report at next year's hearing on the Institute's commitment to support the development of early detection methods, improved surgical techniques, effective chemotherapy, and new drugs for pancreatic cancer and to support public education efforts concerning pancreatic cancer. (p. 119-120)

Action taken or to be taken

An estimated 28,000 cases of pancreatic cancer will occur in the year. An almost equal number of deaths, compared to incidence, will occur from this disease. Although pancreatic cancer is not the most frequent cancer, it is one of the most deadly when it does occur, because early symptoms are non-specific and there are no good early detection methods. The NCI expends about $15 million dollars

yearly for research on pancreatic cancer, and supports over 100 research grants in this disease.

The NCI Director has convened a Pancreatic Cancer Progress Review Group (PanPRG) to sharpen the focus of research programs with respect to pancreatic cancer. The overall goal of the PanPRG is to develop a national research agenda that prioritizes research questions that will need to be addressed to make progress in pancreatic cancer.

Members of the PanPRG, representing basic and clinical researchers from academia, industry, and government, and representatives of the patient advocacy community, have worked together to develop a broad multidisciplinary perspective of ongoing pancreatic cancer research. The PanPRG first met in May 2000. The PanPRG Roundtable meeting, which included over 100 leading members of the pancreatic cancer research and advocacy communities, took place in September 2000. Roundtable participants formulated key scientific questions for the next 5 to 10 years in pancreatic cancer research and informed the deliberations of the PanPRG.
The specific charge given to the PanPRG is to:

- **$** Identify and prioritize scientific needs and opportunities that are critical to hastening progress against the disease
- **$** Define and prioritize the research agenda
- **$** Develop an action plan encompassing both operational and strategic components of the NCI's pancreatic cancer enterprise.

Treatment

Pancreatic cancer tends to metastasize early to the regional lymph nodes and to the liver. A minority of patients with pancreatic cancer will be able to undergo surgery for cure. The detection of metastatic disease is not very good, as documented by the fact that local recurrence occurs in up to 85 percent of patients undergoing curative intent surgery. Survival after surgery can be increased with the use of additional radiation therapy and chemotherapy. With the demonstration that gemcitabine results in a clinical benefit to patients with advanced, unresectable pancreatic cancer, the NCI is supporting clinical trials of adjuvant radiation plus chemotherapy with gemcitabine or 5-fluorouracil.

When pancreatic cancer is too far metastasized to consider curative surgery, treatment options remain limited. Gemcitabine has shown clinical benefit for such patients, but survival remains poor and cure is not possible at this time. New targeted drugs offer hope of improving treatment. Several pharmacologic agents have been shown to interact with some of the signaling cascades thought to be important in the progression of this disease, such as the signaling associated with epidermal growth factor receptor and ras activation. Such agents, as well as vaccines and antiangiogenesis agents are currently in early clinical trials supported by the NCI. In these trials, imaging or tissue endpoints are encouraged in order to ascertain whether the drug is interacting with its intended molecular target.

More traditional treatments are also under study in NCI-supported clinical trials. These include intraperitoneal drug administration, combination studies of chemotherapy drugs or of chemotherapy with

radiation therapy, and a Phase III trial to compare the effectiveness of surgery to remove the pancreas and a portion of the small intestine with or without removing lymph nodes, followed by radiation and chemotherapy. Results of these trials will help guide the development of future therapies.

Translational Research

The NCI currently supports two Specialized Programs of Research Excellence, or SPOREs in Gastrointestinal Cancer. One, University of Nebraska, concentrates entirely on pancreatic cancer. The second, Johns Hopkins University, devotes 50 percent of its resources to pancreatic cancer. The major purpose of these multidisciplinary SPOREs is to increase knowledge of the biology of pancreatic cancer and to increase translation of this knowledge into clinical use. Together, these two projects represent about $3.5 million in total cost. Both SPOREs are pursuing significant developmental therapeutics and early diagnosis and detection research activities. SPOREs also concentrate on finding new genetic markers for pancreatic cancer.
Many investigator-initiated studies contribute to the knowledge of the biology of pancreatic cancer. Such studies include investigation of the role of DNA-damaging agents and antioxidants in high risk patients with inflammatory diseases such as pancreatitis, the role of growth factors, cytokines and other signaling molecules and pathways in the normal and cancerous pancreatic cells, development of animal models that simulate pancreatic cancer formation in humans, and the role of mutated genes such as ras, DPC4, MUC 4 and others as they are discovered.
A PA was issued by the NCI Division of Cancer Treatment and Diagnosis and the Division of Cancer Prevention to support pilot studies of novel markers or innovative assays for the early detection, assessment of prognosis or prediction of response to treatment of cancers.

In addition NCI sponsors a number of pancreatic cancer clinical trials by grants to individual investigators in hospitals and academic institutions; by grants to cancer centers and large multi-center research consortia; by collaboration with pharmaceutical and biotechnology firms, and within its intramural programs. These trials range from small-scale early testing of novel agents or new combinations to very large-scale and definitive randomized trials that can establish the value of a new intervention and include studies of all types, including treatment, prevention, screening and early detection, supportive care, symptom management, and others. There are currently 51 clinical trials in pancreatic cancer of which 38 are NCI sponsored.

In summary, the increasing knowledge of the cellular and molecular biology of pancreatic cancer has provided insights that, if developed further, could result in better and longer survival for patients with this disease. Understanding the biology of pancreatic cancer formation and progression is critical not only for the development of new targeted, and hopefully efficacious, drugs for treatment, but also for the possible development of new strategies for early detection and agents for molecular imaging. Imaging of cancers is very important to progress in many cancers, including pancreatic cancer, and has been designated as an Extraordinary Opportunity by the NCI, supported in the Bypass Budget.

Item

Plant based medicinal products -- The Committee supports the need to accelerate the development and commercialization of plant-based medicinal products and encourages the NCRR to consider collaborating with plant scientists and companies in Hawaii to responsibly use that State's unprecedented biodiversity in developing new, health-enhancing products. (p. 171)

Action taken or to be taken

Since 1955, the NCI has been exploring nature as a source of potential new anticancer drugs, and some of the best drugs available, such as paclitaxel (taxol7), topotecan and irinotecan (semisynthetic derivatives of camptothecin) are derived from plants collected by the NCI in collaboration with the USDA between 1960 and 1982. During this period, 35,000 plant samples (including parts, such as leaves, stems, bark, etc.) were collected, including 5,924 samples from Hawaii. Two hundred seventy-four of the Hawaiian samples showed activity in the then current screens, and one of these, Hymenocallis littoralis , yielded the agent, pancratistatin, which advanced to preclinical development and is still of some interest to extramural investigators.

Since 1986, the NCI has been performing plant collections in over 25 countries worldwide, located mainly in tropical and sub-tropical regions, through contracts with U.S.-based botanical organizations. In 1996, collections were started in the continental United States. Over 55,000 plant samples have been collected and extracts are being made available to the global scientific community for testing against all human diseases. Provision of the extracts is subject to the signing of Material Transfer Agreements protecting the rights of all parties, in particular, those of the countries from which the plants were collected. Several potential anti-HIV agents have been discovered, and one of these, calanolide A, isolated from a plant collected in Sarawak, Malaysia, is in Phase II clinical trials. These contract collections are continuing in Africa, Madagascar and Southeast Asia, and those currently being performed in the continental U.S. are being expanded to include all U.S. Territories. In addition drug discovery, mainly from plants, is being promoted through establishing direct collaborative agreements with qualified research organizations in over ten countries, including Australia, Brazil, China, Costa Rica, Mexico, New Zealand, Panama, and South Africa.

Through the National Cooperative Drug Discovery Group programs, the NCI provides grant support to academic institutions that collaborate with pharmaceutical companies in drug discovery and development from natural sources. Since 1986, 17 awards have been made for the investigation of natural products collected from many countries worldwide. The plant-derived commercial anticancer drug, topotecan, was developed through this program. Grant support is provided to individual investigators engaged in natural products research through other mechanisms, such as R01, R29, SBIR and STTR grants.

The NCI supports the International Cooperative Biodiversity Group (ICBG) program, administered by the Fogarty International Center (FIC), which promotes drug discovery mainly from plants collected in developing countries. Grants are awarded to U.S. Academic institutions collaborating with organizations in developing countries and the pharmaceutical industry. The ICBG program is also

supported by other NIH institutes, including the National Institutes of Allergy and Infectious Diseases (NIAID), Mental Health (NIMH), and Drug Abuse (NIDA), and the National Heart Lung and Blood Institute (NHBLI), as well as the National Science Foundation and the USDA.

Complementary and Alternative Medicine and Dietary Supplements

In 1999, ODS, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), made two grant awards to the University of California at Los Angeles and the University of Illinois at Chicago establishing Dietary Supplement Research Centers with an emphasis on botanicals. The major goal of the awards is to foster interdisciplinary research promoting the scientific study of botanicals, particularly those available as dietary supplements.

In FY 2000, funds have been allocated to expand the number of centers and encourage collaboration between agricultural research institutions and biomedical research institutions. NCCAM, FIC, NCI, NHBLI, NIDA, the National Institute of General Medical Sciences (NIGMS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), the National Institute of Environmental and Health Sciences (NIEHS), and the Office of Research on Women's Health (ORWH) have joined ODS in supporting this initiative, depending on the relationship of the proposals to the various institute and center missions.

In addition to collaborating with ODS in establishing Dietary Supplement Research Centers, NCCAM, in collaboration with NIDDK, has issued a Request for Applications (RFA) to support Small Business Innovation Research and Small Business Technology Transfer projects that could lead to the development of appropriate standardized, botanical products as reference reagents for clinical and basic research.

NCCAM has also issued a Program Announcement (PA) supporting developmental studies to establish the methodological feasibility and strengthen the scientific rationale for proceeding to full-scale randomized clinical trials on the use of traditional indigenous systems of medicine as practiced in the United States.

The NCI has formed the Office of Cancer Complementary and Alternative Medicine (OCCAM) to investigate the clinical efficacy of complementary and alternative products used in cancer prevention and treatment. OCCAM has just released an RFA to NCI-designated cancer centers for applications to support pilot project research in complementary and alternative medicine, including plant-based medicinals. OCCAM and NCCAM will work jointly in promoting programs to support this research.

Scientists and companies in Hawaii may apply for support through all the programs mentioned above and in fact, it was expected that the University of Hawaii would compete for a Dietary Supplement Research Center award. Hawaii-based scientists have received support from the NCI in the area of

marine natural products research, and the Bishop Museum has been involved in several projects with the NCI.

Submission of proposals from the Hawaiian scientific community in response to RFAs and PAs, and through the usual grant mechanisms, will be welcome. In September 2000, NCI issued a Request for Proposals for a contract for the collection of plants from all U.S. territories. These collections could encompass Hawaii, and extracts of Hawaiian flora could be made available to the extramural scientific community for testing against all human diseases through the NCI extract distribution programs.

Item

Prostate Cancer -- . . . . The Committee urges the NCI and other institutes to aggressively increase efforts that will lead to the development of new treatments, new preventives, and new interventions with the potential to improve or extend the lives of men touched by prostate cancer. (p. 120)

Action taken or to be taken

Please refer to pages NCI-70 through NCI-85 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- . . . . The Committee encourages NCI to develop methods to identify those patients at risk of progression who would benefit most from aggressive therapy, while sparing low-risk patients the morbidity resulting from aggressive treatment of slow-growing disease. The Committee also encourages NCI to carry out clinical trials that will determine whether yearly screening for prostate cancer using the PSA blood test will decrease mortality from prostate cancer. (p. 120)

Action taken or to be taken

Please refer to pages NCI-70 through NCI-85 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- . . . . The Committee encourages NCI to test new systems that will identify the best trials, improve trial planning, speed trial activation, and improve availability of trials to patients. The Committee encourages NCI to implement programs to assist investigators in academia and in small businesses in getting compounds with promise for treatment and prevention of prostate cancer into clinical testing using NCI's existing development resources. Several key treatment questions must be addressed. The Committee urges NCI to initiate clinical trials that will optimize hormonal and chemotherapeutic approaches for the most common clinical presentations of prostate cancer. (p. 120)

Action taken or to be taken

Please refer to pages NCI-70 through NCI-85 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- . . . . The Committee urges NCI to conduct studies to identify risk factors for prostate cancer in several populations, including African-Americans and Chinese. The Committee also encourages NCI to study the associations of dietary patterns with prostate cancer, and variations in the role of diet in different racial and ethnic groups. (p. 121)

Action taken or to be taken

Please refer to pages NCI-70 through NCI-85 of this document for NCI's response to this significant item regarding Prostate Cancer.

Item

Prostate Cancer -- The Committee is encouraged by NCI's collaborations with the Department of Defense in fighting this devastating disease, and urges NCI to continue to strengthen and expand its prostate cancer research portfolio. The Committee further expects the NCI to accelerate spending on prostate cancer, and consult closely with the research community, clinicians and patient groups to identify promising new avenues of basic and clinical research. (p. 121)

Action taken or to be taken

Please refer to pages NCI-70 through NCI-85 of this document for NCI's response to this significant item regarding Prostate Cancer.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2000 Amount Authorized	2001 Estimate	2002 Amount Authorized	2002 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$3,675,828,000	Indefinite	$4,108,893,000
National Cancer Institute	Section 417B	42§286a-8	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	62,100,000	b/	68,310,000
Total, Budget Authority				$3,737,928,000		$4,177,203,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2001 (P.L. 106-554).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	$2,010,439,000	$1,998,616,000	$2,010,439,000	$1,981,351,000 2/
Rescission				0
1994	2,142,122,000	2,082,267,000	2,082,267,000	2,076,382,000
Supplemental				
1995 3/	1,967,709,000	1,917,929,000	1,917,929,000	1,919,419,000 4/
Rescission				-5,600,000
1996	1,994,007,000 3/	2,251,084,000	2,184,467,000 3/	2,251,084,000
Rescission				-2,654,000
1997	2,060,392,000 3/	2,385,741,000	2,102,949,000 3/	2,381,399,000 5/
1998	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 7/
Rescission				-2,005,000
2002	4,177,203,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes enacted administrative reductions of $16,060,000; $9,933,000; and $139,000.
3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
4/ Excludes enacted administrative reductions of $901,000; $116,000; and $1,482,000.
5/ Excludes enacted administrative reductions of $1,095,000 and $38,000.
6/ Reflects a decrease of $7,301,000 for the budget amendment for bioterrorism.
7/ Excludes enacted administrative reduction of $781,000.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Office of the Director	712	766	789
Center for Cancer Research	1,396	1,573	1,620
Division of Cancer Biology	50	59	62
Division of Extramural Activities	92	115	118
Division of Cancer Treatment and Diagnosis	198	212	218
Division of Cancer Prevention and Treatment	88	104	107
Division of Cancer Control and Population Sciences	116	155	160
Division of Cancer Epidemiology and Genetics	142	166	171
Total, NCI	2,794	3,150	3,245
FTEs not included above	(6)	(5)	(5)

Funds to support these FTEs are provided by Cooperative Research and Development Agreements

FISCAL YEAR	Average GM/GS Grade
1998	11.1
1999	11.2
2000	11.2
2001	11.2
2002	11.2

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Program Administration

Detail of Positions

GRADE	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
ES-6	1	1	1
ES-5	4	4	4
ES-4	2	2	2
ES-3	2	2	2
ES-2	2	2	2
ES-1	1	1	1
Subtotal	12	12	12
Total - ES Salary	$1,523,389	$1,561,474	$1,600,511
GM/GS-15	261	266	271
GM/GS-14	300	323	333
GM/GS-13	286	308	318
GS-12	349	376	391
GS-11	256	276	288
GS-10	15	16	16
GS-9	203	218	235
GS-8	149	161	164
GS-7	175	188	197
GS-6	44	47	47
GS-5	48	52	55
GS-4	33	36	39
GS-3	10	11	11
GS-2	5	5	5
GS-1	1	1	1
Subtotal	2,135	2,284	2,371
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	62	63	63
Senior Grade	30	30	30
Full Grade	21	22	22
Senior Assistant Grade	2	2	2
Assistant Grade	0	0	0
Co-Step	0	0	0
Subtotal	116	118	118
Ungraded	707	767	775
Total permanent positions	2,205	2,391	2,486
Total positions, end of year	2,970	3,181	3,276
Total full-time equivalent (FTE) employment,end of year	2,794	3,150	3,245
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$126,949	$130,123	$133,376
Average GM/GS grade	11.2	11.2	11.2
Average GM/GS salary	$60,542	$62,753	$65,045

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

New Positions Requested

	FY 2002		
	Grade	Number	Annual Salary
Administrative Asst	GS 9	1	$36,656
Administrative Officer	GS 12	2	53,156
Administrative Program Assistant	GS 8	3	33,187
Bio Lab Tech	GS 9	2	36,656
Bio Lab Tech	GS 7	3	29,966
Biologist	GS 12	4	53,156
Biologist	GS 11	4	44,352
Biologist	GS 9	3	36,656
Chemist	GS 12	2	53,156
Chemist	GS 11	1	44,352
Chemist	GS 9	2	36,656
Clinical Trials Specialist	GS 12	3	53,156
Communications Specialist	GS 11	2	44,352
Computer Specialist (Informatics)	GS 14	2	74,697
Computer Specialist (Informatics)	GS 13	2	63,211
Computer Specialist (Informatics)	GS 9	3	36,656
Epidemiologist	GS 15	1	87,864
Epidemiologist	GS 13	2	63,211
Geneticist	GS 15	1	87,864
Health Disparities Specialist	GS 14	1	74,697
Investigator (Tenure Track)	AD -	3	80,000
Lab Manager	GS 13	2	63,211
Lab Manager	GS 9	2	36,656
Manager Admin Resource	GS 14	1	74,697
Medical Officer	GS 15	2	87,864
Medical Officer	GS 14	2	74,697
Medical Officer	GS 13	4	63,211
Medical Technologist	GS 9	3	36,656
Microbiologist	GS 12	2	53,156
Microbiologist	GS 11	1	44,352
Molecular Biologist	GS 14	1	74,697
Molecular Biologist	GS 12	2	53,156
Molecular Biologist	GS 9	1	36,656
Office Automation Clerk	GS 4	3	21,623
Procurement Tech	GS 7	3	29,966
Secretary	GS 7	3	29,966
Secretary	GS 5	3	24,192
Senior Clinical Investigator	SBRS	1	113,000
Senior Clinical Investigator	GS 14	3	74,697
Senior Molecular Biologist	SBRS	2	116,776
Senior Research Chemist	GS 15	1	87,864
Senior Research Geneticist	SBRS	1	117,936
Senior Research Virologist	SBRS	1	118,000
Technology Development Admin Specialists	GS 11	4	44,352
Total Requested		95	