February 1997

"STATEMENT OF THE DIRECTOR FOR FISCAL YEAR 1998"

Department Of Health And Human Services
National Institutes of Health
National Cancer Institute

Richard D. Klausner, M.D.

This past year we recognized the 25th anniversary of the 1971 National Cancer Act. It has been an historical year as we sought to evaluate this Nation's investment in cancer research and assess the fruits of that investment. This fall we were able to announce that for the first time since we began to track the constant rise in cancer mortality rates over 60 years ago, we had encouraging news. Sometime around 1990, we appeared to have reached the peak in the mortality rate and for the past 5 years, overall age-adjusted mortality rates have fallen. This includes the most common causes of cancer deaths, lung, colorectal, breast and others. We believe that these encouraging changes are the result of prevention, especially declining tobacco use among American adults, early detection and better therapy--all of which are the fruits of research. The burden of cancer is not shared equally within our society. African Americans, for example, experience a 20-30 percent excess rate of cancer death compared to white Americans. The latest mortality data include a significant drop in cancer death in African Americans, that may be larger than the decrease reported for white Americans. Despite this good news, we continue to evaluate the causes for differential cancer incidence and mortality among different racial and ethnic groups. Overall, these statistics, I believe, tell us that our investment is paying off. They tell us what we can accomplish but that we have much more to do.

Today, over 10 million Americans are cancer survivors. The majority of these were diagnosed with cancer more than 5 years ago. In recognition of the many unanswered questions that long-term cancer survivors face and the need to do research to answer questions about medical and psychological consequences, late recurrences, second cancers and long-term effects of treatment, we are initiating a series of funding initiatives in this area.

Our fundamental discovery goal is to ultimately develop effective interventions that reduce the incidence, morbidity and mortality of cancer. There is no one intervention or even one type of intervention that will successfully conquer the many diseases we call cancer. Our approach must be open and broad-based, aimed at identifying those at risk and those with modifiable risk factors, developing sensitive and predictive means of early detection, learning to finally correctly diagnose each cancer so that the diagnosis predicts the course of disease and dictates the choice of therapy. Cancer is a disease in which one of the trillions of cells in our bodies gradually changes over time. That cell is a crucible in which the interacting players of genes and environment meet and produce the alterations that drive the behavior of each cancer.

There are two ways to search for the causes of cancer. We can look from the outside and scan the cell's environment for agents of cellular change. Some have been easy to identify, such as the chemicals in tobacco which cause multiple cancers and are responsible for 30 percent of all cancer deaths, or the sexually transmitted virus, Human Papilloma Virus, responsible for 90 percent of cervical cancers. Environmental factors that can alter the risk of cancer include diet, outside factors such as environmental chemicals and radiation and the internal factors such as hormones and the chemical and physical soup within each cell. We currently employ scores of epidemiologic studies to search for connections between all of these factors and specific cancers, to search out potentially avoidable risks for particular cancers.

More recently, we have learned to look within the cell at the differences between individuals in order to explain why external risks are magnified or reduced in different people. The identification of specific cancer susceptibility genes that explain inherited risks continues to be a focus of discovery. Over the past year, scientists have identified new inherited susceptibility genes for skin cancer and the locus for the first prostate cancer susceptibility gene. We have moved to push beyond the discovery of these genes to fund studies to evaluate the interaction of these genes with environmental, dietary and hormonal factors; to establish more precisely the risk associated with specific alteration in specific genes; and to evaluate chemical or surgical prevention strategies for high risk individuals. We have designed a new research infrastructure called the Cancer Genetics Network aimed at linking centers of excellence throughout the country to work together as a network to develop protocols for critical studies in individuals at genetic risk for cancer to address the many issues that this new aspect of oncology is creating.

The ability to look at genetic changes in cancer cells offers an interesting twist to the search for external causes of cancer--a type of reverse epidemiology. Scientists are now exploring whether the fingerprint of particular types of carcinogens can be found, much like the thief that leaves incriminating evidence at the crime scene, to help us use the effects of environmental carcinogens to identify the culprits. This has been recently demonstrated for one of the carcinogens in tobacco smoke, as well as for a carcinogen that causes liver cancer found contaminating certain foods.

Prevention in part, explains the drop in cancer mortality rates and prevention will play an increasingly important role in the future. Prevention studies range from evaluating behavioral intervention against tobacco use and for healthful diets to pharmacologic interventions including drugs that block the actions of hormones to prevent breast or prostate cancer, anti-inflammatory agents to prevent colon and other GI cancers, vitamin derivatives to prevent aerodigestive cancers, and others. In fact, we are testing 24 agents in 78 clinical trials aimed at preventing cancer, approaching it not as an event but as a long and stoppable process.

The identification of infectious causes of cancer provides another type of prevention opportunity. Based on major breakthroughs at the NCI, we have made a commitment to proceed with the development and testing of a multivalent vaccine against cancer causing

strains of human papilloma virus--the first such effort to vaccinate against an agent solely for the purpose of preventing cancer.

Early detection of cancer remains a critical part of increasing survival and enhancing the possibility of cure. The success of early detection depends upon awareness, access and the availability of tests that are sensitive and specific. All of the increase in breast cancer incidence that we saw through the 1980s (now leveled off) was the result of an increased detection of early disease and now 65 percent of breast cancer is found as localized disease compared to less than 40 percent twenty years ago with a 5-year survival rate of 92 percent. On March 27, 1997, the National Cancer Advisory Board (NCAB) issued its recommendations regarding mammography to the NCI. The NCI accepted the NCAB recommendation to recommend regular screening mammograms every one to two years to women ages 40-49 at average risk of breast cancer. Women at higher risk should seek expert medical advice about beginning mammography prior to age 40, and about the screening interval. We are actually engaged in the evaluation of many new imaging techniques for cancer detection and hope to set up a diagnostic imaging research consortium to, for the first time, establish a stable group of investigators to evaluate innovations in cancer imaging. We are vigorously pursuing the development of better mammography, digital mammography, MRI, and digital ultrasound and other non-invasive techniques, as well as powerful new approaches to image analysis to both provide better sensitivity to the detection of breast cancer and to clarify the majority of abnormal mammograms which detect structures that are not breast cancer, thereby reducing the false positive rate of breast cancer screening.

The final component of decreasing cancer mortality is improved treatment. Clinical trials are the means by which we test and establish the best treatment for cancer. We have continued to work with partners to assure that patients have access to clinical trials, strengthening our cancer clinical trials agreement with the Department of Defense and concluding a new agreement with the Veterans Administration to integrate the VA medical system into the NCI clinical trials and cancer centers network. We have embarked on a strategic plan to restructure our clinical trials information system to create a modern informatics base, developed in conjunction with the FDA and the International Committee on Harmonization to develop electronic system for data on adverse events and the use of common toxicity criteria. A single entry clinical data reporting system will greatly facilitate these trials and the pilot testing for this system will be completed by April. These efforts will improve the speed and accuracy of reporting, produce resource savings and remove the impediments of burdensome and cumbersome paperwork.

Critical to enhancing access to clinical trials is available information. We are currently working with patient and consumer groups to rewrite the NCI PDQ information system to be more inclusive of all trials, more user-friendly and comprehensible and more accessible. The NCI Clinical Trials Evaluation Program is currently sponsoring over 750 active clinical trials, including 258 phase I trials this year to test new drugs and therapeutics. These range from a virus engineered to kill only cancer cells, to gene therapy, to immunologic approaches to cancer, to photon-based therapy, and to new small compound drugs directed against the cancer cells or the blood vessels that nourish them.

In addition, hundreds of other trials are conducted at NCI cancer centers and through other funding mechanisms. This past year, 12 new drugs were approved by the FDA for use in cancer and we anticipate over 30 Investigational New Drug Applications in 1997. In the biotechnology industry, over 40 new agents are in clinical trials for cancer. Cancer is the largest single target of this burgeoning industry.

Notable results of clinical trials over the past year include the demonstration of a 30 percent reduction in mortality for adjuvant therapy in stage C colon cancer translating into approximately 4000 lives saved each year and as these benefits may extend to stage B patients, the benefits may be even greater. Interferon has been demonstrated to be of benefit, at least in a significant subset of patients with advanced melanoma. The markedly improved survival of combination chemotherapy with radiation for nasopharyngeal cancer resulted in a cooperative group clinical trial being halted early. Other examples illustrate the incremental advances being made, each adding to improved survival for patients with multiple types of cancer. These trials examine new agents, new combinations of therapy and new ways of delivering therapy such as neo-adjuvant treatment where chemotherapy, for example, is given before rather than after surgery in order to improve surgical success and even to allow less extensive surgery.

One recent therapeutic advance illustrates how cancer therapy is being altered by our new understanding of the molecular characteristics of cancer. Researchers at the NCI, in collaboration with extramural investigators, have been testing new treatment regimens for a particularly aggressive form of lymphoma. A 5-drug regimen resulted in an apparent cure, or long-term remission in about 50 percent of the patients. The remainder either failed to respond or rapidly relapsed. What was different? In virtually all of the relapsed patients, their cancer cells harbored a mutation in the p53 gene, a gene whose loss of function is implicated in over 50 percent of all human cancer. What had been called one cancer was clearly at least two distinct diseases. Recently, the investigators evaluated a newer regimen with three additional drugs and have observed long-term remission, hopefully cure, in 90 percent of all of these patients.

This example illustrates a principle that is guiding a transformation in oncology. We can begin to identify the defining characteristics of any cancer. It is the set of alterations that will define the actual targets for therapy that is designed rather than arrived at empirically and it is the molecular distinctions between cancers that will allow us to tailor therapy to the right disease. In addition, the alterations that distinguish a cancer from a normal cell offer us the set of possibilities for biomarkers for early detection for stealth cancers, such as ovarian, pancreatic, kidney and others. We have made great strides in this critical area of molecular diagnostics but can do more. For that reason, we have embarked on an ambitious project to identify all of the genes expressed in cancer versus normal cells. We call this the Cancer Genome Anatomy Project (CGAP) and its goals are two-fold: 1) to produce a full index of expressed genes for normal, pre-malignant and malignant cells and, 2) to help support the development, dissemination and application of new technologies to apply these indices for the discovery of markers for cancer detection, of discriminators for accurate diagnosis and choice of therapy and of targets for new therapeutics and prevention. CGAP both builds on and is complementary to the Human

Genome Project and is being done through joint intramural and extramural efforts. CGAP has been developed with explicit annual milestones and will be a national resource that all can tap into via the world-wide web. CGAP involves a collaborative effort with the National Library of Medicine and the Department of Energy, as well as with industrial partners.

Connecting the profound advances in basic sciences and epidemiology to the clinic has been referred to as translational research. Over the years, the NCI Cancer Centers Program has been a central component of the development and realization of such research. One of my goals was to fully re-evaluate this program to assure it best rewarded outstanding science and best facilitated translational research at the many institutions capable of contributing to the National Cancer Program. To this end, we commissioned and have received a report from a blue ribbon panel which has proposed significant changes in the guidelines, review processes, definitions and funding policies for a revitalized Cancer Centers Program. We are now in the final stages of revising the program to incorporate most of the recommendations of the review group.

Finally, the NCI is committed to fulfilling its role within the larger National Cancer Program and we have strengthened and enhanced our many interactions and collaborations with other agencies and private organizations, with the research and clinical communities, with advocacy organizations and the public.

The challenges and opportunities before us are great. To address these, Mr. Chairman, the budget request for the National Cancer Institute for FY 1998 totals $2,217,482,000, an increase of $61,066,000. I am pleased to be able to appear before the committee and look forward to answering any questions.