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"Fiscal Year 2000 President's Budget Request for the National Cancer Institute"

Statement of
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Mr. Chairman and Members of the Committee:

This has been a year of real progress in cancer research. For the past three years in appearing before you, I have emphasized the dramatic changes in the science and technology of cancer research, changes that we at the National Cancer Institute (NCI) are fostering and facilitating. We are all convinced that these changes can and will be applied to reducing the burden of cancer and that they will accelerate the continuing reduction in cancer incidence and mortality that we first reported two years ago.

Advances in Cancer Treatment and Prevention

This year, I would like to illustrate some of the tangible advances made just over the past year in the prevention and treatment of specific cancers. Of course, this only represents a fraction of what we do in order to understand the causes and nature of cancer. It is fitting to report on clinical trials results in this, the 50th anniversary of the introduction of the modern, randomized controlled trial. In many ways, these trials are the culmination of the research pipeline. They establish the real value of innovation and change the practice of medicine to benefit people with or at risk for cancer. Let me highlight a few examples which illustrate several important themes. First, we are beginning to approach the prevention of cancer in addition to its treatment. Second, we are continuously optimizing even our conventional therapies in order to improve patient outcome. Third, we are beginning to tailor therapy to more precise diagnostic categories of cancer, which is made possible by a new age of molecular diagnostics. Fourth, we have begun to test novel therapies targeting the molecular machinery of cancer, heralding the future of cancer prevention and treatment.

This year, we reported the successful results of the first major cancer prevention trial carried out by one of the NCI-funded clinical trials group, NSABP. It is an example of a mechanism-based intervention aimed at preventing this common cancer. By treating women who have elevated risk for breast cancer with a partial estrogen antagonist, tamoxifen, a 50% reduction in incidence of breast cancer was observed over the course of the study. There was a 70% reduction in breast cancer incidence for those breast cancers expressing estrogen receptors, whereas there was no change in incidence of breast cancers that lacked this receptor which is the molecular target for the drug. This study showed that we can reduce the risk of breast cancer. Much remains to be studied and

tamoxifen is far from perfect in terms of its effectiveness and its side effects. It is, however, an important and landmark beginning.

The optimization of existing therapies continues to be an important approach to improving the outcome for cancer patients. Years of clinical trials to optimize chemotherapy regimens for children with acute lymphocytic leukemia (ALL) have resulted in a current cure rate of 75-80%. About 20% of children with ALL have poor prognostic characteristics and a much bleaker outcome. Results of a new trial using a modified chemotherapy regimen has resulted in a 70% drop in the rate of treatment failures in these high risk children under 10 years of age; these children have a 5-year event-free survival of 84% with this new regimen.

Nasopharyngeal cancer is relatively rare in the United States but quite common in Asia. Chinese American men have a 15-20 fold higher rate of this cancer than white American men. While nasopharyngeal cancer has been known to be responsive to radiotherapy or chemotherapy, a trial comparing the former to a combination of radiotherapy plus Cis-Platin + 5-FU was stopped early because of profound benefit. The 3-year survival in the radiotherapy alone group was 47%, whereas, the combined group had a 78% 3-year survival, and a 60% reduction in mortality.

Differential Response to Therapy

Why some patients respond to a given therapy and others, with ostensibly the same disease, do not, is a central puzzle we are beginning to solve. One likely explanation is that the responders actually have a different disease than the non-responders. In a recently reported series of studies, one explanation for outcome differences in breast cancer has apparently emerged. About 30% of breast cancers make too much of a protein called, HER2/neu. These cancers appear to be more aggressive and new studies showed that these cancers respond significantly better to elevated doses of anthracycline drugs than cancers that don't overexpress this protein. This conclusion came from the analysis of several breast cancer treatment trials that were not originally designed to answer the question about the role of HER2 in the response to therapy. These subsequent analyses were done in order to explain why some women responded better to higher doses of therapy while others did not. Critical studies such as these require that scientists who have new ideas and new technologies have access to tissue samples that are linked to important clinical data. Over the past year, we have created a new approach to funding more of these important correlative studies and have developed a new set of mechanisms to expedite interactions between researchers with good ideas and researchers with access to tissue banks.

One of the ultimate goals of cancer research is to uncover the molecular machinery of each cancer in order to target prevention and therapies to that machinery. The great hope is that such targeted approaches will prove to be both more effective and less toxic than our current approaches. This past year, based upon clinical trials results, the FDA approved the first two monoclonal antibodies, Herceptin® and Rituximab®, for the

treatment of cancer. Each is directed at a molecule expressed on the surface of specific types of human cancer.

Herceptin® is directed against HER2, a protein discovered almost 20 years ago, and proposed as a potential therapeutic target almost 15 years ago. This new drug was tested this year against metastatic breast cancer, the most deadly and least treatable stage of this disease. When such patients are treated with the drug taxol, only 16% experience a clinical response of tumor shrinkage. However, with the addition of Herceptin®, 42% of patients have anti-tumor responses and these women experience a statistically significant prolongation of survival. As hoped for, Herceptin® added relatively little toxicity. Now, we are working with the company that developed Herceptin® to rapidly expand the evaluation of this agent in earlier stages of breast cancer and in the treatment of other cancers, such as ovarian, which overexpress the target of this drug.

Non-Hodgkin's lymphoma is newly diagnosed each year in over 55,000 Americans. It is one of the few cancers whose incidence has been rising. Fifty percent of those diagnosed will die of their disease and, as with so many cancers, we need new, more effective and less toxic therapies. Twenty years ago, basic immunologic research identified a molecule, CD20, specific to the surface of B lymphocytes which was also highly expressed on the surface of most lymphomas. An antibody directed against this molecule was shown to be able to kill cells and thus began a 15-year odyssey to engineer an anti-CD20 antibody which could be used in treatment. Last year, such an engineered antibody, Rituximab®, was approved by the FDA. It is becoming the treatment of choice for patients with low grade lymphoma. It is as effective at inducing remission as chemotherapy but with very little toxicity. As with all such advances, we do not stop there but use these findings as a stepping stone for further development. Multiple clinical trials are underway to broaden the cancer targets for Rituximab®, to combine it with chemotherapy and, in a very promising development, to arm the antibody with radionuclides. Early phase II studies with I^{131} -labelled anti-CD20 show it to be five times more effective at inducing long-term disease-free survival than the best available chemotherapy. These promising results will need to be validated in definitive clinical trials with the hope that this new example of molecular therapy will profoundly alter the outlook for these cancer patients.

These examples are just a sampling of recent clinical trials culminations. Our clinical trials not only examine new treatment regimens but also evaluate ways of reducing toxicity, decreasing pain and suffering and improving the short and long-term quality of life for cancer survivors.

We are now instituting the first major reform and restructuring of the NCI national clinical trials system since it was established 40 years ago. The goal of this restructuring is to make this national resource function even better by:

1. creating a new peer review system that will allow and encourage any scientist to propose the best ideas for large-scale clinical trials,
2. providing a complete menu of clinical trials options that will be available to all patients and all participating physicians,

3. improving the operating characteristics of the clinical trials system, reducing barriers to participation, speeding the conduct of the trials and enhancing the efficiency and effectiveness of these important studies,
4. moving to adequately fund this research system, and
5. improving our communication processes to provide everyone with comprehensible information about clinical trials.

These changes will mean more clinical trials culminations over the next several years. This fiscal year, we have provided a 30% increase in funding to our national clinical trials system to enable these changes. Among other changes, this will allow us to increase the number of new trials initiated and to address more questions within all of our trials.

We have also restructured our clinical trials capabilities within our intramural research program. This coming year, we intend to initiate definitive clinical trials to test the benefit of novel vaccine therapies directed against non-Hodgkin's lymphoma and melanoma, the two major cancers whose incidences are rising in the U.S.

Clinical trials are the culminations of the research pipeline that must be filled, if we are to build on the progress made to date.

Improving Cancer Detection

Two years ago, we set up the Cancer Genome Anatomy Project (CGAP) to systematically identify the gene expression patterns that characterize human cancer. It is time now to begin to apply the gratifying progress of this project in order to develop new molecular classification schemes for patients with cancer. If successful, this will fundamentally change our approach to diagnosis, to the choice of therapy and to our ability to predict patient outcome. The Director's Challenge is a $50 million program to challenge the scientific community to accomplish just that and to deliver a new generation of diagnostic and prognostic practices to patients with cancer.

We are anxious to realize the dream of having sensitive and accurate tests to detect cancer early when it is most curable. CGAP has enabled the discovery of literally hundreds of potential markers for cancer over the past two years. For example, one year ago, we knew of no potential unique marker for ovarian cancer. Today, CGAP has provided 400 candidates ready to be tested. With the new funds we received this year, we are establishing the Early Detection Research Network to, for the first time, create a national research infrastructure to rapidly develop and test such potential markers for cancer. We are hoping that such tests will give us accurate, predictive and simple blood tests for all types of cancers.

The ability to detect, diagnose and evaluate cancer by imaging is a critical part of our approach to these diseases. We have never had a rapid way to evaluate the constantly changing technologies within the context of clinical trials. To remedy that, this year, we established the diagnostic imaging research network. This network will begin by

addressing important clinical questions, such as defining the role of CT scanning and magnetic resonance imaging in the staging of women with cervical cancer.

There is a great need to assure that we fill and expand the pipeline of new agents for the prevention and treatment of cancer. This past year, we initiated a new program called RAID (for Rapid Access to Interventional Development) in order to fund the rapid transition of new therapeutic reagents from the laboratory to the clinic after rigorous peer review in order to identify the most promising proposals. In its first year, RAID will fund 20-30 new therapeutics for such rapid development. Due to its initial success, we hope to be able to expand RAID and are also adding a new program called RAPID to offer the same process for agents aimed at preventing cancer.

Progress against cancer takes place through both the development of knowledge and of new technologies. New technology often enables the discovery of new knowledge as well as the application of that knowledge to people with, or at risk for, cancer. Evaluating, reviewing and funding research aimed at acquiring new knowledge requires different approaches than for technology development. For these reasons, this year, we created a new grant mechanism called the Phased Innovation Award which is already proving to be a highly sought after award tailored to technology development.

New Efforts in 1999

New resources over this past year has enabled us to initiate a wide range of new research programs and projects. These include new programs in tobacco-related research, initiatives in basic biobehavioral and health communications research and a variety of programs aimed at more rapidly translating basic discoveries to clinical testing in prevention, detection, diagnosis and treatment.

The progress we are making in cancer research does not equally reach all Americans. Minorities and the underserved often have higher incidence and mortality rates and poorer outcomes. The NCI supports an extensive research program aimed at identifying and explaining the unequal burden of cancer in our diverse society. This year, we will expand our support of cancer control and research infrastructures in minority and underserved communities as one component of addressing the unequal cancer burden.

We have improved and enlarged our programs to monitor cancer burden and to identify environmental factors that may contribute to that burden. This year, we will publish, for the second time, a 25-year survey of cancer mortality rates, cancer-by-cancer, for all 3000 U.S. counties. This will serve as the basis for our ongoing search for clues to environmental, regional and occupational causes of cancer.

A two-year strategic effort to redesign our training and career development programs aimed especially at strengthening clinical research, multi-disciplinary training and training opportunities for minorities and the underserved, has begun to be implemented with a 30% increase in dollars aimed at training and career development in FY99 over FY98.

Our Cancer Centers Program which was redesigned two years ago, has grown to include 5 new centers in parts of the country which had not had NCI-designated cancer centers over the past two years and we expect to fund 2-4 new centers in the current year.

Finally, a 15% increase in dollars in the 1999 research projects grants pool is enabling us to fund approximately 400 additional projects and a total of 1229 competing grants this year, including our AIDS research program.

This year, the President has proposed a 2.4% increase in the NCI cancer budget to $2,732,795,000. This will allow us to continue to support the many initiatives that I have outlined for you. Funds for AIDS research are included with the request of the Office of AIDS Research.

The activities of the NCI are covered within the NIH-wide Annual Performance Plan required under the Government Performance and Results Act (GPRA). The FY 2000 performance goals and measures for NIH are detailed in this performance plan and are linked to both the budget and the HHS GPRA Strategic Plan which was transmitted to Congress on September 30, 1997.