January 1, 1992 to January 31, 1994

# President's Cancer Panel

# Report of the Chairman

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

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U.S. Department of Health and Human Services

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National Cancer Institute

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# PRESIDENT'S CANCER PANEL

National Cancer Program • National Cancer Institute


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The President
The White House
Washington, D.C. 20500

Dear Mr. President:

The Health Omnibus Extension Act of 1988 requires the Chairman of the President's Cancer Panel to report annually to you on the status of the National Cancer Program. Accordingly, I am pleased to submit the attached report covering 1992 and 1993.

I was appointed to the Panel in 1991 and currently serve as a member and Chairman. Dr. Henry Pitot was appointed to the Panel in 1992 and will serve a three-year term through February 1995, pending replacement or reappointment. Mrs. Nancy Brinker completed her appointment to the Panel in February 1993 and was replaced by Ms. Frances M. Visco, Esquire, who will serve as a member until 1996.

Mr. President, within five years cancer will surpass heart disease as the leading cause of death in the United States. Fully one-third of the people will develop cancer in their lifetime. This year alone, more than one million Americans will be diagnosed, and approximately one-half million will die.

In the Panel's previous communications to your office, we have emphasized that many Americans have not benefitted from cancer research advances made to date; that poor Americans continue to have a lower cancer survival rate compared to Americans of higher socioeconomic status; and that we continue to face questions of access to care and, if access can be obtained, of insurability.

Although future health care reform may address many of the concerns faced by poor and other medically underserved Americans, we, as members of the Federal Government, must face a more fundamental problem than treating the afflicted -- that problem is educating and empowering people to protect their own health. Indeed, adequate health care and appropriate preventive and curative strategies for cancer will only be fully realized with the involvement of each American in his or her own health care.

Since becoming Chairman of the Panel, I have continually stressed that ensuring equitable access to and appropriate delivery of care should be part of the role of all Federal, state, and local organizations with health-related activities. This view, I believe, reflects the intent of the Congress and the President at the time of the passage of the 1971 National Cancer Act when they indicated that the full power of the President, the Cabinet, and the Legislative Branch of the Government would be invoked in conducting a war against cancer. However, it was not truly recognized at that time that this war on cancer would not be fought as a conventional war by armies of researchers, but as a guerrilla war waged in every home in the nation, and as a war based on prevention and early detection rather than research and treatment alone.

With this theme as a central tenet, the Panel has, since my last report to you, examined the issues of cancer in underserved populations, the role of poverty as a determinant of disease, and the impact of cancer as a family issue. Cancer-related voluntary organizations, which reach and serve the American population in ways the Federal Government simply cannot, were reviewed to assess how best to coordinate governmental activities to maximize the capabilities of these organizations. A special review was also done on basic research, screening, detection, and treatment options in prostate cancer.

Other areas explored by the Panel included the interrelated issues of cancer research and technology transfer as research is increasingly exported for public applications, governmental cooperation with industry and academia, and the declining interest of talented young scientists in health research careers due unstable funding expectations. In this context, we reviewed the University of California SPORE (Specialized Program of Research Excellence) at San Francisco, which focuses on translating bench research in breast cancer into clinical applications and conversely, clinical observations into research questions. It also provides a unique opportunity for patient advocates to participate with researchers and clinicians in designing and implementing research efforts.

In view of the issues raised in these meetings and as directed by Congressional mandate, the Panel also convened a series of meetings to evaluate the National Cancer Program and to assist in formulating goals for the Program in the year 2000. The first of these meetings combined a review of measures of progress and the achievements of the National Cancer Program with invited critiques from well-known scientists in the areas of mechanisms of cancer induction and progression, molecular medicine, diagnosis and early detection, treatment, prevention, and control. The final meeting in 1993 examined those regions within the United States where mortality due to cancer is excessive and where it is clear that there are obstacles to reaching the affected populations. In



January 1994, the Panel reviewed cancer-related research activities of a wide range of Federal agencies to assess the extent of coordination, gaps, and duplication of effort.

A separately chartered advisory panel established at the request of then Vice President Quayle, the President's Cancer Panel Special Commission on Breast Cancer, met intensively over 18 months to develop its recommendations on progress and barriers in the fight against breast cancer. That report, Breast Cancer: A National Strategy - A Report to the Nation, was presented directly to Hillary Rodham Clinton in October 1993 and will not be discussed here.

Similarly, a subcommittee of the National Cancer Advisory Board (NCAB), convened at the request of both houses of Congress and on which I had the honor of serving as a member ex officio, met from September 1993 to September 1994 to further assess progress of the National Cancer Program since its inception and make recommendations for its direction into the next century. The subcommittee's report, Cancer at a Crossroads: A Report to the Nation, was transmitted to the Congress in September 1994 with the full concurrence of the NCAB.

The recurrent theme throughout all these meetings has been the need to provide access to and insurance coverage for cancer prevention, diagnosis, treatment, and control for all Americans; the need to further delineate the determinants of cancer causation through continued support for basic and applied research; and the need to coordinate the cancer-related research and cancer care activities of the Federal, state, and local government as well as private and voluntary organizations.

Therefore I make the following recommendations:

- Continue and augment funding of basic research through the National Cancer Institute and accelerate application of basic research discoveries through translational research to develop improved cancer prevention, detection, treatment, and supportive services.

- Pinpoint the obstacles preventing access to existing cancer prevention, diagnosis, treatment, and support for all Americans and delineate the roles of the National Cancer Institute and the other public and private sector participants in the National Cancer Program in ameliorating these barriers.

- Mount a joint cooperative effort among Federal, local, and voluntary agencies to educate the American public regarding its options in cancer prevention and health care access.

- Coordinate research efforts across Federal, local, and voluntary organizations in a joint offensive against cancer.

I and the other members of the President's Cancer Panel are privileged to play a role in monitoring and guiding the National Cancer Program and remain committed to its goals of reducing death and suffering from cancer in this country and throughout the world.

Sincerely,

Harold P. Freeman

Harold P. Freeman, M.D.
Chairman

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# REPORT OF THE CHAIRMAN: 1992-1993

## INTRODUCTION

One in three people in the United States will develop cancer in his or her lifetime, and one in five will die of the disease. This year, approximately 1.25 million new cases of cancer will be added to the over eight million Americans already living with a diagnosis of cancer.

To fulfill the commitment to the American people made by the National Cancer Act to reduce suffering and death due to cancer, and to meet the responsibilities entrusted to the President's Cancer Panel to monitor and appraise the National Cancer Program, the Panel continued its examination of barriers to achieving Program goals.

In 1971, the authors of the National Cancer Act recognized that cancer research advances would derive from a broadly based effort and charged the National Cancer Institute (NCI) Director with coordinating "all the activities of the National Institutes of Health relating to cancer with the National Cancer Program." In this capacity, the NCI Director was charged, "with the advice of the National Cancer Advisory Board, [to] plan and develop an expanded, intensified, and coordinated research program encompassing the programs of the NCI, related programs of the other research institutes, and other Federal and non-Federal programs." Over time this charge has been modified through various bills, but today the scope of the National Cancer Program still encompasses "...related research programs of other national research institutes ..." [PHS Act, Sec. 411] which is reflected by the interrelatedness and coordination of cancer research across all NIH institutes.

The Charter of the President's Cancer Panel (PCP) stipulates that the Panel shall "monitor the development and execution of the activities of the National Cancer Program and ....delays or blockages in the rapid execution of the Program shall immediately be brought to the attention of the President." We have attempted to identify and examine those issues critically during the past two years. In addition, this report incorporates by reference the recently completed report of a National Cancer Advisory Board subcommittee formed to carry out a request from the Congress to identify barriers to and opportunities for progress against cancer in the next ten years. This effort, which in part parallels the charge of the PCP, has reached conclusions consistent with and supported by those of this Panel.

Significant advances have been made in basic, clinical, and applied cancer research; the potential to apply the advances to reduce morbidity and mortality, and improve survival and quality of life for the cancer patient and family has been recognized. However, when the NCI reviews the annual cancer mortality and morbidity statistics as part of its assessment of program efficacy under the National Cancer Program, it still finds an age-adjusted rate of increase in deaths due to cancer from 1970 to 1990 of approximately seven percent (National Center for Health Statistics data). This age-adjusted rate accounts for both population increases and ages of the U.S. population.

According to the NCI Surveillance, Epidemiology, and End Results Program (SEER) data, cancer incidence has increased by approximately 18 percent from 1970 to 1990, while survival has

increased by only four percent during the same period. Six cancers appear to be responsible for 65 percent of these grim statistics -- breast, lung, prostate, colorectal, urinary/bladder, and non-Hodgkin's lymphoma -- these cancers seem to unjustly target the underserved: minorities, the elderly, the impoverished, and the undereducated. [Statistics provided at the PCP meeting of September 22, 1993.]

In the years between establishment of the PCP through the 1971 National Cancer Act and 1993, refined therapeutic interventions including systemic chemotherapies and less radical or invasive surgical procedures have improved longevity and the quality of life for some patients, and improved non-surgical options have limited or prevented organ impairment and protected an individual's dignity. We have begun to treat cancer patients more as survivors and less as victims of their disease and have begun the necessary, but slow, recognition that the cancer survivor is another partner in the National Cancer Program.

The President's Cancer Panel, consisting of myself as Chairman, Dr. Henry Pitot of Madison, Wisconsin, and Mrs. Nancy Brinker of Dallas, Texas, began our consideration of the issues identified above in 1992; Mrs. Brinker was replaced by Ms. Frances Visco, Esquire, of Philadelphia, Pennsylvania in May 1993.

# I. MEETINGS OF THE PRESIDENT'S CANCER PANEL

## A. Cancer Research and Technology Transfer in the 1990s

The first 1992 Panel meeting, held in San Francisco at the University of California (UCSF) in February, focused on "Cancer Research and Technology Transfer in the 1990s." Testimony was heard on the preparation of American institutions necessary to meet the technology transfer issues of the future, essential training of the next generation of cancer researchers who will develop and apply new knowledge, and the role of the NCI-designated Comprehensive Cancer Centers in this process. Experts provided testimony on the current status of relationships between academic institutions and industry, the role and effectiveness of academic institutions in transferring research technology into practical application, problems in recruiting and training basic researchers, and the need to train physician-scientists.

The Comprehensive Cancer Centers are central to our efforts to link research to the community, meld basic and clinical research, and improve cancer prevention and control through community outreach initiatives based on basic and clinical research findings. Comprehensive Cancer Centers offer a multi-disciplinary approach to research into all aspects of cancer, especially by linking scientific and technological advances to raise the standard of patient care. There were only three such Centers in 1971; today there are 27 Comprehensive Centers. Counting the Clinical and Consortium Cancer Centers, there are currently 54 NCI-designated Cancer Centers at which Americans can receive state-of-the-art cancer care. Increasingly, these Centers are strengthening their focus on prevention research, while maintaining their emphasis on basic science and research on diagnosis and treatment. Approximately half of NCI funding for peer-reviewed research supports work conducted at the Cancer Centers. A new grant mechanism, the P50 core grant program or Specialized Programs of Research Excellence (SPORE), has been introduced to facilitate and speed



the translation of basic research findings into clinical application through clinical trials or population studies focused on specific cancer sites: breast, gastrointestinal, lung, and prostate.

Speakers emphasized the need for career incentives to entice basic and clinical researchers to undertake the challenge of cancer research and to train and support translational researchers who bridge the gap between the bench and the bedside, thereby turning laboratory observations and knowledge into improved cancer therapies and technologies. Equally evident was the challenge to the NIH to ensure that its investigator-initiated, peer reviewed grant process can adapt from its traditional funding of basic laboratory science to less easily evaluable research in cancer prevention and control, and to the complexity of clinical research. Addressing these issues will be crucial to ensure that basic research tools can be transferred flexibly to the arena of application. Likewise, clinicians must be afforded the opportunity and, in fact, enticed to bring questions raised by their empirical observations back to the field of basic research. Moreover, the patient must be considered both the endpoint and beginning of cancer research. Only through the development of synergy -- with open, reciprocal communication between patient, clinician, and basic scientist -- will the flow of innovation in science translate into reduced cancer mortality and morbidity.

A second area considered was the protection and facilitated transfer of intellectual discoveries to attract industry financial and intellectual support for the practical application of basic and clinical observations, i.e., the translation of a "good idea" into a therapy or technology that can be tested against rigorous industrial and Federal standards to assess its readiness for application to human disease. A balance must be struck between protecting intellectual property rights in Federally-funded research, ensuring fair and reasonable costs of the new technology to the American public which has paid for the research, and providing a reasonable profit margin that should accrue to the private industry concerns involved. Again, the focus must be on "end user" -- the patient -- and how the natural competitiveness of American science should be used to benefit people with cancer and those at risk.

A final theme of the meeting was that of training. Young clinicians and basic scientists face ever-greater competition to obtain initial grant support. This pressure fosters either specialization within very narrow, though sound scientific fields, or the migration of discouraged young investigators away from research. To overcome this barrier to evolution of the next generation of innovative scientists, opportunities to fund truly innovative research must be fostered; opportunities must exist for clinicians to experience basic research and for basic researchers to understand the potential for application of their discoveries. The development of the SPORE grant program is one step along this pathway.

## B. Cancer in Minority Populations: Opportunities and Obstacles

In June 1992, the Panel met at the American Health Foundation in New York to examine "Cancer in Minority Populations: Opportunities and Obstacles." This hearing focused on identifying characteristics and needs of the underserved that contribute to excess cancer mortality in this population. Twelve speakers, including epidemiologists, educators, public health specialists, and physicians, presented testimony on epidemiologic observations of minority populations, including mortality statistics and psychosocial, behavioral, and cultural considerations influencing nutrition, tobacco and alcohol use; primary and secondary school observations of how the education process

fails to address primary prevention education strategies and how this can be overcome; and finally, how a smoking control research initiative can be applied through community mobilization, intervention, and evaluation. For example, lung cancer mortality will be lowered only through prevention -- by eliminating tobacco or educating our young people to resist the sociocultural lure of the cigarette. To achieve this goal, we must not fail to realize that cancer occurs in people, under certain human circumstances that develop from social and cultural bases. As we develop educational interventions, we must ensure that they are truly accessible, i.e., culturally sensitive and reflective of the human circumstances in which they must be applied. To reach underserved populations who are disproportionately represented in the growing cancer mortality statistics, programs may well need to be administered through church or community groups, at night, or on weekends when the participants can attend, or with inducements that might include necessary transportation, child care, or even financial support.

## C. The Role of Voluntary Organizations in the National Cancer Program

The third Panel meeting of 1992, held in Bethesda, explored "The Role of Voluntary Organizations in the National Cancer Program." These organizations have contributed to the Program since its inception and are currently helping to shape the future of health and health care for the nation. Ten speakers representing eight organizations described their organizational interests in cancer research, treatment, education, and prevention. They discussed their missions, funding levels, program or research activities, and made recommendations for improving communication among themselves and with the Government, particularly with regard to high priority research areas with critical funding needs.

Many of the speakers emphasized that primary cancer prevention is now more important than ever and that voluntary organizations are addressing this need. Research and funding to examine the dynamics of human behavior as a factor in cancer control were identified as a critical need, as was the need to develop primary school-based prevention efforts through a comprehensive health education program in tobacco control and nutrition.

An underlying theme of this meeting was improved communication, collaboration, and coordination among Federal, state and private organizations. Several speakers suggested that a comprehensive education program should be developed under the leadership of the Department of Education rather than targeted funding of single issues which may have limited or less enduring impact. In addition, advocacy by patients, organizations, and agencies is becoming a potent force in cancer prevention, control, and treatment; one function of advocacy organizations is to represent the interests of cancer survivors, including those in underserved populations, who often face discrimination on the basis of disease. Voluntary organizations can provide support and advocate for change in ways that Government agencies cannot.

As at other meetings, speakers emphasized the need for consistent support of career development opportunities for the next generation of cancer researchers. Training should be comprehensive, with a "bench to bedside" reciprocal approach that will enable researchers to develop culturally and behaviorally sensitive, effective cancer prevention and control strategies as well as new treatments. These observations were based on recognition of the need for coordinated community application of research discoveries and the fact that many such applications result from basic research. Better



communication among health care organizations to eliminate duplication of effort and foster complementary funding of research efforts must also be achieved.

## D. Prostate Cancer

The final meeting in 1992 was also held in Bethesda and reviewed issues associated with prostate cancer. For this purpose, the Panel convened 17 nationally recognized experts to discuss unanswered questions about prostate disease and report on the status of prostate cancer research, screening, early detection, and treatment. The meeting opened with a presentation to Dr. Peter Scardino of a Certificate of Designation for the Prostate Cancer Spore at Baylor College of Medicine as the Matsunaga/Conte Prostate Cancer Research Center. Mrs Matsunaga attended this meeting and a letter from Mrs. Conte was also read.

Speakers described issues and trends in basic research and their implications for preventing prostate cancer, improved early detection through the use of biomarkers to assess risk levels and chart disease progression, and improved treatment and management options. Genetic susceptibility, genetic and environmental interactions in disease initiation and progression, promising lines of investigation, and potential new treatment agents for prostate cancer were discussed.

The Panel also revisited issues from previous meetings, such as the impact of prostate cancer on the elderly and the startling prostate cancer mortality statistics for African Americans. Differences in incidence between, white, African American and native Asian populations were highlighted as a reflection of cultural, genetic, environmental, or dietary differences among these populations. Observations to date suggest that survival differences are most likely due to the extent of disease at diagnosis and may reflect cultural, educational, health care access, and patterns of care differences.

Firm evidence of familial predisposition to prostate cancer was presented. Studies of families with a high incidence of the disease may lead to identification of the genes involved in familial prostate cancer and high-risk individuals who should receive more intensive screening.

The advantages and the limits of prostate specific antigen (PSA) screening were discussed, as was the need to demonstrate that such screening reduces mortality. Concentrating screening on high-risk groups -- men over 45 years of age who are either African American or have a first-degree relative (e.g., father, brother) with prostate cancer -- will help in assessing potential benefits of screening. A long-term, large population screening intervention is being conducted by the National Cancer Institute to address this issue. This trial is designed to screen men aged 60 to 75.

A chemoprevention trial of finasteride (Proscar), a drug that blocks androgen production, is being developed as a ten-year study of 18,000 men over age 54 years; its primary objective is to compare prostate carcinoma incidence in Proscar-treated patients versus patients given a placebo. Secondary objectives of this study are to observe the effect of finasteride on prostate cancer grade and stage at diagnosis; to examine long-term morbidity or toxicity associated with finasteride; to examine its effect on benign prostatic hyperplasia; and to address quality of life issues. Finasteride is already approved by the Food and Drug Administration for treatment of benign prostatic hyperplasia.

Another participant in the meeting, Dr. Phillip Gorden, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), described the Institute's significant contributions in endocrine, urologic, and other research, but particularly in the study of benign prostatic hyperplasia. Two urologic centers conducting work on hyperplasia and cancer, the George O'Brien Kidney/Urologic Centers, are co-funded by NCI and NIDDK, reflecting the two institutes' joint efforts and combined scientific cultures relating to prostate disease. Finally, the benefit of anti-androgen therapy to inhibit prostate disease progression was discussed as was the categorization of prostate cancer as a prototype of hormone-dependent tumors.

Participants recommended research to: develop more and better markers for prostate cancer prognosis; improve pre-operative prediction of adverse findings in poorly differentiated disease; address quality of life issues; evaluate treatment benefit relative to screening, detection, and enhanced survival; and improve local disease control.

### E. The Breast Cancer SPORE at UCSF

The Panel also held four meetings in 1993 to continue its exploration of issues raised at previous meetings and to gather testimony pursuant to its appraisal of the National Cancer Program. The first meeting took place at the University of California, San Francisco, and reviewed translational research efforts of the UCSF SPORE in breast cancer. Enlarging on the theme of technology transfer initiated in February 1992, the Panel examined early efforts of the SPORE grantees to gather a critical mass of researchers, patients, and advocates to translate basic science to clinical research, develop applications for preventing, detecting, and treating breast cancer, and identify new basic research efforts.

The SPORE supports the critical practice of investigator-initiated research in a manner that encompasses the totality of the cancer problem, requires interdisciplinary support and cooperation, includes observations of environmental effects, and addresses quality of life issues. The SPORE seeks to develop new molecular and cellular markers for predicting breast cancer prognosis, and to use that information to improve patients' quality of life by treating patients with poor prognosis with aggressive chemotherapies and avoiding their unnecessary use in women with favorable prognoses. The SPORE also seeks to bridge institutional departmental barriers through better communication, and foster the identification of new intervention targets based on the joint clinical and basic science analysis of cellular and genetic lesions. Defining disease from this dual perspective will also facilitate rational design of preventive and dose-intensive treatment strategies based on identified disease markers. The SPORE also works to improve cooperation between academia and industry to exploit clinical observations, analyzed at the genetic level, and speed development of anti-cancer drugs.

### F. Cancer and the Family

In conjunction with the American Cancer Society (ACS) meeting to mark the tenth anniversary of its Psychosocial and Behavioral Research Program, the Panel held a session on "Cancer and the Family" to examine the effects of a cancer diagnosis on the patient and other cancer survivors -- the family care givers and children.



Cancer has a tremendous social impact on the family that can include additional expenses, complete loss of income, loss of insurance, and inability to find employment. All of these socioeconomic variables compound the physical and emotional drain cancer places on the patient and his/her family. For example, "failure-to-thrive" symptoms are not uncommon among healthy newborns in families that have experienced disease or death of a family member. The ability of a family member to cope with cancer-related socioeconomic problems can affect the cancer patient's coping mechanisms as much as disease-related factors. Cancer-related stresses may affect biological parameters such as immune response in patients and family members. In particular, spouses who are the primary care givers frequently need psychosocial support that may extend beyond the endpoint of cure, with its element of uncertainty, or even beyond death and grieving. These issues are compounded by both the success of certain cancer interventions in prolonging survival and by current health care economic realities that return patients to the family setting more rapidly, and more quickly transfer the burden and cost of supportive care to the family.

In general, there is a need to integrate services addressing family stress and coping into routine cancer care and to examine the impact of cancer on the individual and on marital pairs, the parent-child dyad, and the overall household level of functioning and morbidity. Few intervention studies have been done to examine these issues and many of those that have been done suffer from problems related to population size, ill-defined methodology, or use of unstandardized instruments. Nonetheless, these studies indicate a clear need for age-appropriate educational materials to explain cancer and its implications to children and adolescents, to systematically assess patient and family functioning during the course of illness, and to develop interventions that accommodate socioeconomic and cultural differences.

Future health care reform must recognize cancer-related family morbidity and provide necessary education, counseling, and financial support. In addition, as genetic markers of disease continue to be identified, issues regarding access to genetic information, the need for psychosocial counseling, and possible needs for prophylactic medical care must be resolved and included in any health care reform program.

### G. Evaluating the National Cancer Program

As part of the NCI response to the mandate contained in the 1993 appropriations language, and as appropriate under its statutory mission, the President's Cancer Panel heard testimony on "Evaluating the National Cancer Program" in Bethesda on September 22, 1993. This meeting combined a sobering commentary on cancer statistics, a review of progress made by the National Cancer Program, and invited criticism from well-known experts representing various disciplines.

It is clear that significant progress has been made over the last decade in understanding environmental factors and their contributions to cancer induction and in grasping the synergistic and progressive effect that chemicals (e.g., tobacco, nitrosamines, heterocyclic amines, polyaromatic hydrocarbons) have in causing genetic alterations. In addition to a better understanding of environmental carcinogenesis, breakthroughs have been made in understanding the genetics of cell repair, identifying positive and negative regulators of cell growth, elucidating the step-wise process theory of cancer onset and progression, developing strong molecular and animal models for understanding how specific genes are associated with cancer, and in cancer epidemiology. This

improved understanding of the mechanisms of cell structure and growth is the foundation for virtually all areas of cancer research.

In the area of molecular medicine, the importance of the step-wise theory of cancer progression was emphasized. This theory has been used to help identify tumor-specific oncogenes or biomarkers of disease, which may ultimately lead to improved cancer screening and prevention. Armed with this knowledge of cell function, researchers are now better prepared to determine how cellular defects result in abnormal cell growth and tumor progression and where intervention potential exists. Similarly, understanding the molecular nature of these events now permits the application of traditional physical chemical principles in the field of structural biology, e.g., computer design of efficacious therapeutics is now possible based on knowledge of structural determinants.

Continuing development of technologies such as the polymerase chain reaction (PCR) offer the possibility to detect minimal disease, occult residual tumors, and molecular endpoints as measures of therapeutic response with previously unmatched sensitivity. The field of gene transfer technology opens the door to gene therapy and the replacement of defective genes. Equally important are recent advances in the field of immunology and the understanding of how cells are involved in the immune response. Genetic engineering has provided the promise of targeting immunotoxins to abnormal proteins found in cancer cells while leaving normal cells undamaged.

In the areas of diagnosis and early detection, advances in imaging technology, serologic markers, and statistical analysis have presented opportunities to detect and treat tumors earlier, to examine them *in vivo* and while actively growing, and to use image-guided interventions to reduce the need for exploratory surgery and decrease the impact of necessary surgery. Serologic markers such as prostate specific antigen (PSA), CA-125 in ovarian cancer, and HER-2/neu in breast cancer, have contributed to patient management through non-invasive tests for cancerous or precancerous cell functions. Meta-analysis now permits the combination of data from small studies to support health care decision-making (e.g., regarding application of biomarkers), while multivariate analysis reveals the significance of individual biomarkers. Dynamic monitoring is being used to track changes in tumor markers as a measure of treatment efficacy.

Surgical interventions in cancer treatment have become less invasive with the advent of limb sparing and organ conserving techniques. Improved diagnosis and detection enables treatment to begin earlier, affording many patients choices other than radical surgery. Improved outcomes from radiotherapy are due not only to new technology, but to the recognition that effective local therapy can achieve maximum tumor control while limiting overall toxicity. Chemotherapy is now a viable tool both before surgery to reduce tumor size and after surgery to prevent or reduce the likelihood of recurrence.

Greater understanding of the molecular interactions within cells has led to the development of new drugs, multidrug therapy regimens, and an improved understanding of multidrug resistance. Cytokines and growth factors as regulators of cell growth are used not only to treat cancer, but to limit treatment side effects, reduce the use of antibiotics, and reduce inpatient time. Bone marrow transplantation is now a treatment choice for a growing number of cancers. Advances in treating pain and nausea associated with cancer have contributed to improved quality of life for many cancer patients, but much work is still needed in this area.



Clearly, prevention is the key to reducing cancer incidence and mortality. Advances in prevention have resulted from cooperation among the various disciplines to identify suspect cancer causes and develop interventions. There have been significant developments in the area of diet, nutrition, and cancer, including establishment of the first NCI intramural nutrition laboratory, promulgation and implementation of nutritional guidelines by the NCI, publication of the Surgeon General's Report on Nutrition and Health, and the implementation of food labeling. The first prospective intervention trials demonstrating the relationship between diet, nutrition, and cancer were conducted in the last decade, but the role of diet in cancer development is far from resolved.

Two areas of basic research have special implications for cancer prevention: chemoprevention using natural or synthetic agents to reverse, prevent, or suppress carcinogenesis in healthy or high risk individuals; and the use of biomarkers to identify individuals at risk for disease and assess the efficacy of chemoprevention. The greater importance accorded viruses as a causative factor in human cancer has opened another avenue for public health intervention.

Finally, advances in cancer control have been mixed. Progress in tobacco control has been remarkable and is largely the result of public advocacy. Adoption of screening guidelines and better dissemination of information, particularly among the underserved and poor women, have resulted in greater awareness of opportunities for breast and cervical cancer screening.

To take advantage of knowledge gained through cancer risk factor research, the health care system must now shift its emphasis from diagnosis and treatment to prevention and management. Meeting this challenge will be complicated by the need to accommodate special populations with differences in disease outcome, access to health care, ability to pay for care, and response to motivational strategies used under the current health care system. It should be noted that the National Cancer Program has already made some progress in this area. Information dissemination strategies and interventions have been and continue to be developed to bridge cultural barriers. Patient and public interest in cancer prevention has never been higher, and both heightened awareness of cancer risk factors and positive behavior changes are apparent in some population groups. Interest in quality of life issues, rehabilitation, and supportive care have expanded as a strong advocacy movement has developed.

Communication of cancer information through NCI's Cancer Information Service (CIS) and the Physician Data Query System (PDQ) has had a positive impact on both the public and on health professionals, while the SEER (Surveillance, Epidemiology, and End Results) Program remains a primary source for tracking and evaluating cancer incidence and mortality.

Despite improved technologies and their more widespread application, the National Cancer Program still faces an incidence rate that has risen by 18.3 percent between 1973 and 1990 and a mortality rate that has grown by 6.7 percent, despite an improved relative survival rate (from 49 to 53 percent). Breast, lung, prostate, and colorectal cancer still are responsible for 57 percent of cancer cases and 55 percent of deaths. Recent statistics have indicated that the United States may be experiencing a encouraging slight, but perceptible, downward trend in the incidence of some cancers, however, current data indicate a significant differential between African Americans and whites. Cancer incidence among African Americans is eight percent higher and mortality is 35 percent higher; African American males have a 50 percent higher cancer mortality rate than white males.

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In the areas of diagnosis and early detection, advances in imaging technology, serologic markers, and statistical analysis have presented opportunities to detect and treat tumors earlier, to examine them *in vivo* and while actively growing, and to use image-guided interventions to reduce the need for exploratory surgery and decrease the impact of necessary surgery. Serologic markers such as prostate specific antigen (PSA), CA-125 in ovarian cancer, and HER-2/neu in breast cancer, have contributed to patient management through non-invasive tests for cancerous or precancerous cell functions. Meta-analysis now permits the combination of data from small studies to support health care decision-making (e.g., regarding application of biomarkers), while multivariate analysis reveals the significance of individual biomarkers. Dynamic monitoring is being used to track changes in tumor markers as a measure of treatment efficacy.

Surgical interventions in cancer treatment have become less invasive with the advent of limb sparing and organ conserving techniques. Improved diagnosis and detection enables treatment to begin earlier, affording many patients choices other than radical surgery. Improved outcomes from radiotherapy are due not only to new technology, but to the recognition that effective local therapy can achieve maximum tumor control while limiting overall toxicity. Chemotherapy is now a viable tool both before surgery to reduce tumor size and after surgery to prevent or reduce the likelihood of recurrence.

Greater understanding of the molecular interactions within cells has led to the development of new drugs, multidrug therapy regimens, and an improved understanding of multidrug resistance. Cytokines and growth factors as regulators of cell growth are used not only to treat cancer, but to limit treatment side effects, reduce the use of antibiotics, and reduce inpatient time. Bone marrow transplantation is now a treatment choice for a growing number of cancers. Advances in treating pain and nausea associated with cancer have contributed to improved quality of life for many cancer patients, but much work is still needed in this area.



Clearly, prevention is the key to reducing cancer incidence and mortality. Advances in prevention have resulted from cooperation among the various disciplines to identify suspect cancer causes and develop interventions. There have been significant developments in the area of diet, nutrition, and cancer, including establishment of the first NCI intramural nutrition laboratory, promulgation and implementation of nutritional guidelines by the NCI, publication of the Surgeon General's Report on Nutrition and Health, and the implementation of food labeling. The first prospective intervention trials demonstrating the relationship between diet, nutrition, and cancer were conducted in the last decade, but the role of diet in cancer development is far from resolved.

Two areas of basic research have special implications for cancer prevention: chemoprevention using natural or synthetic agents to reverse, prevent, or suppress carcinogenesis in healthy or high risk individuals; and the use of biomarkers to identify individuals at risk for disease and assess the efficacy of chemoprevention. The greater importance accorded viruses as a causative factor in human cancer has opened another avenue for public health intervention.

Finally, advances in cancer control have been mixed. Progress in tobacco control has been remarkable and is largely the result of public advocacy. Adoption of screening guidelines and better dissemination of information, particularly among the underserved and poor women, have resulted in greater awareness of opportunities for breast and cervical cancer screening.

To take advantage of knowledge gained through cancer risk factor research, the health care system must now shift its emphasis from diagnosis and treatment to prevention and management. Meeting this challenge will be complicated by the need to accommodate special populations with differences in disease outcome, access to health care, ability to pay for care, and response to motivational strategies used under the current health care system. It should be noted that the National Cancer Program has already made some progress in this area. Information dissemination strategies and interventions have been and continue to be developed to bridge cultural barriers. Patient and public interest in cancer prevention has never been higher, and both heightened awareness of cancer risk factors and positive behavior changes are apparent in some population groups. Interest in quality of life issues, rehabilitation, and supportive care have expanded as a strong advocacy movement has developed.

Communication of cancer information through NCI's Cancer Information Service (CIS) and the Physician Data Query System (PDQ) has had a positive impact on both the public and on health professionals, while the SEER (Surveillance, Epidemiology, and End Results) Program remains a primary source for tracking and evaluating cancer incidence and mortality.

Despite improved technologies and their more widespread application, the National Cancer Program still faces an incidence rate that has risen by 18.3 percent between 1973 and 1990 and a mortality rate that has grown by 6.7 percent, despite an improved relative survival rate (from 49 to 53 percent). Breast, lung, prostate, and colorectal cancer still are responsible for 57 percent of cancer cases and 55 percent of deaths. Recent statistics have indicated that the United States may be experiencing a encouraging slight, but perceptible, downward trend in the incidence of some cancers, however, current data indicate a significant differential between African Americans and whites. Cancer incidence among African Americans is eight percent higher and mortality is 35 percent higher; African American males have a 50 percent higher cancer mortality rate than white males.

In contrast, the single most remarkable advance of the past two decades has been the reduction in cancer mortality among children and young adults. These differences illustrate that the relationship between cancer incidence and cancer mortality is by no means straightforward. It varies by cancer type due in part to interventions now possible across the continuum of cancer care (i.e., screening, detection, diagnosis, treatment, supportive/rehabilitative care) and to environmental and lifestyle differences.

Overall, current cancer statistics reflect the need for more prevention research and the scientific community cannot yet ascertain how long it will take to fully reverse the upward trend in cancer incidence. It has learned, however, that the battle against cancer will not be won in the laboratory alone, and that scientific advances must be translated into improved cancer prevention and cancer care that is accessible to people in all socioeconomic environments.

As an invited critic, Dr. Philip Landrigan noted that the work place offers both ideal and less than ideal environments for cancer research. Generally, working populations are well-defined groups with some exposures that may come from point-sources. The estimated number of cancers caused directly by occupational exposure range from two to eight percent and the NCI estimates that occupational factors may contribute to up to 38 percent of all cancers. Occupational settings can be useful for studying the efficacy of primary prevention strategies; by preventing exposure to single substances, effects on cancer incidence, morbidity, and mortality can be assessed.

As pointed out by Dr. David Rall, Scientist Emeritus, National Institute of Environmental Health Science (NIEHS), however, individuals are exposed to a myriad of agents and other cancer promoting factors in their work, home, and other public environments. The occupational carcinogens still of greatest concern are asbestos, silica dust, formaldehyde, chlorinated hydrocarbons, polychlorinated biphenyls, dioxin, furan, solvents, and pesticides. Of equal or greater concern are the majority of synthetic chemical compounds developed during the past 50 years that have never been tested for carcinogenicity or toxicity. However thoroughly we may investigate a particular agent, more data are needed to evaluate the ambient level of pollutants in air, food, and water, and their effect on total human carcinogen exposure. In addition, standardized instruments are needed to facilitate the conduct of epidemiological studies of environmental carcinogen effects, and medical and scientific personnel require training to obtain effective exposure histories. Until these objectives are achieved, tracing a direct cause-effect relationship between environmental factors and cancer will remain difficult.

Dr. Robert DeWitty of Howard University, echoed the frequently heard concern that special populations are often underserved by cancer prevention and control efforts that fail to take into consideration questions of accessibility, cost, and the basic human right to dignity. Only when interventions reflect a sensitivity to these concerns will it be possible to reach these populations. Intervention will no longer be the sole province of scientists and physicians as patients and consumer advocates take a larger role in research. Groups such as the Women's Health Network, represented by Ms. Cindy Pearson, are already involved in many Federally-funded projects, and are actively advocating the importance of an integrated approach to prevention and treatment that takes into account a patient's social, economic, and physical environment.

Similarly, Ms. Ellen Stovall of the National Coalition for Cancer Survivorship pointed out that the number of cancer survivors (defined as people living with a cancer diagnosis, including those in



treatment) is increasing and that survivors have a unique perspective that must be shared with the research community and the public. Little research has been done on the medical and psychosocial interventions needed by survivors or the impact of psychosocial factors on disease outcome. The survivor population can provide these insights if incorporated into the health care and research processes.

Death must still be acknowledged as an inevitable outcome of certain cancers. As noted by Dr. Michael Levy of the Fox Chase Cancer Center, cancer care may be viewed as a continuum that includes prevention, cure, long-term palliation, short-term palliation, psychological support, and research. The growing numbers of people with advanced cancer underscores the need to integrate palliation into the spectrum of comprehensive cancer care. Effective pain control is essential to limit the psychological impact of cancer on the patient and family. Hospice, as a concept and as a group of services, is an integral part of cancer care and needs to become a fully accepted part of the health care system. Continued improvements in cancer pain management will require the education of physicians, other cancer care providers, patients, and families.

Mr. Berkley Bedell, formerly of the House of Representatives, suggested that the National Cancer Program currently gives insufficient consideration to unconventional or complementary cancer therapies. He stressed the need to devote more attention to assessing the efficacy of such alternative treatments.

## H. Cancer Statistics and Chronic Disaster Areas

The final meeting of 1993, held in New York, addressed the concept of cancer "chronic disaster areas," -- geographic areas in which cancer mortality approaches levels seen in third world countries. Nine speakers representing different disciplines and areas of the country discussed unique problems in delivering cancer care to socially distinct populations whose customs and social environments compound the usual difficulties posed by economic, access, education, and cultural issues.

Areas with similar rates of mortality were compared, such as Harlan, Kentucky and Harlem, New York, whose principal common characteristic is poverty. With poverty come issues of access to care, due not solely to discrimination, but to physical limitations imposed by distance and transportation problems, family responsibilities, and cultural biases. Similar findings were described in North Carolina, Louisiana, and parts of New Mexico, where cancer mortality among the rural and metropolitan poor exceeds expectations based on incidence rates.

Patients in "chronic disaster areas" present with more advanced and more aggressive disease due in part to delayed detection. For example, cervical cancer is a largely curable disease, but patients from these areas frequently die from cervical cancer because they are not screened at regular intervals. They are not screened because they do not know about screening procedures, cannot reach screening sites, or have family or work obligations that prevent timely screening. These are issues based in poverty, lack of education, and cultural values that are far different from those of middle class America. Because of their unique cultural environments, reaching these populations requires gaining the trust of the community and building on cultural strengths to implement prevention and control strategies. Several presenters provided evidence that using trusted

community members, usually women, can provide a gateway into the local culture and facilitate health care delivery.

## I. Role of Government Agencies in the Research Mission of the National Cancer Program

On January 31, 1994 the Panel met to assess the role and activities of governmental agencies in the research mission of the National Cancer Program. Cancer research is not the sole province of the NCI; numerous Federal, state, and local agencies conduct and support cancer-related research consistent with their distinct missions. The Panel has been concerned, however, that these activities lack national coordination that would make optimal use of the resources committed to cancer-related research and best benefit the American people. A related concern is that agencies outside of the NCI or other NIH institutes may not view their cancer-related research activities as an integral part of the National Cancer Program.

Eighteen speakers representing 15 Federal agencies and two state government agencies described their cancer-related research activities, the status of working relationships with the NCI and other agencies, including collaborative efforts and data sharing, and made recommendations for future research emphases at their agencies and for the National Cancer Program in total.

Much of the cancer-related research conducted by Federal agencies other than the NCI involves risk assessments of environmental or worksite exposures, including pesticides, industrial chemicals, pollutants from automobile exhaust and tobacco smoke, high- and low-dose radiation, and environmental hormone sources. In most cases, the goal of the research is not specifically to achieve and measure reductions in cancer incidence and mortality, but to support regulatory decisions and standard setting which will lead to safer environments or to develop new measurement or other technologies. Some of the research, however, has objectives similar to cancer research typically funded by the NCI. For example, the National Institute of Standards and Technology (NIST) is developing a serum biomarker test to monitor high levels of 16-alpha hydroxyesterone, which has been associated with increased susceptibility to breast cancer. Another NIST effort is aimed at developing a biochemical test for markers of ataxia telangiectasia (AT), which is associated with increased radiation sensitivity and multiple primary cancers in affected persons. A reliable test for AT will help identify individuals needing frequent cancer screening, and will help ensure that AT patients with cancer receive treatment that accommodates their special radiation sensitivity.

Testimony presented indicated that collaboration and information sharing among agencies varies widely. For example, National Institute of Occupational Safety and Health (NIOSH) scientists perform quantitative risk assessments on potential hazards (e.g., benzene, cadmium, radon) on which regulatory decisions by the Occupational Safety and Health (OSHA), Environmental Protection Agency (EPA), and other agencies are based. State agency representatives indicated, however, that their working relationships and collaborations with NCI and other Federal agencies involved in cancer research are minimal or absent. Other testimony suggested that there is significant duplication of effort and lack of communication between Federal agencies conducting research with implications for cancer prevention and control.

Among the important recommendations offered by speakers for better coordination of cancer-related research and other activities were: (1) include state organizations in National Cancer Program planning, (2) improve compatibility of cancer registry and other related data, i.e., SEER, Center for



Disease Control and Prevention's National Program of Cancer Registries, state cancer registries, secondary data sources such as Medicare files, (3) coordinate actions in all areas of government, including legislative action, to remove incentives to produce and use tobacco, (4) use the community health center network to extend the reach of cancer clinical trials to underserved populations, and (5) clearly designate responsibility for research into specified areas to avoid duplication of effort and facilitate collaboration.

# II. NCI ACTIVITIES

## A. Control, Prevention and Detection

The National Cancer Institute is charged with executing a program of basic and applied research in cancer control. This effort is closely coupled with cancer incidence, mortality, and morbidity surveillance and monitoring.

During 1992 and 1993, NCI in partnership with the American Cancer Society (ACS) began the implementation phase of the American Stop Smoking Intervention Study (ASSIST) through state and local health departments and the ACS volunteer organizations. A ten-year tobacco control demonstration project, ASSIST targets minority and underserved sectors of the population, combining media campaigns, advocacy for policy change, and smoking cessation support through the health care system, schools, work sites, and other community channels.

The 5-A-Day program is a joint effort with the Produce for Better Health Foundation to encourage Americans to eat five or more servings of fruits and vegetables each day. Current grants awarded to state health agencies, universities, and Cancer Centers are designed to evaluate the efficacy of this approach in schools, work sites, and community settings.

The Appalachian and Minority Leadership Initiatives on Cancer were implemented. The National Black Leadership Initiative on Cancer, the National Hispanic Leadership Initiative on Cancer, and the Appalachian Leadership Initiative on Cancer established 56 regional coalitions to address barriers limiting access to quality cancer control services, to advance the Healthy People 2000 goals, and to promote smoking cessation, diet modification, early detection, and treatment among African American, Hispanic, and Appalachian populations.

The Native American Women's Cancer Initiative was developed to identify and address barriers to culturally appropriate cancer control in screening, diagnosis, treatment, follow-up, and rehabilitation related to cancers that disproportionately affect Native American women.

The NCI participates in the NIH Women's Health Initiative, specifically through a dietary intervention study, e.g., testing the ability of dietary fat reduction to lower the risk of breast, colorectal, and cardiovascular disease in postmenopausal women. An ongoing NCI pilot study is testing the feasibility of achieving dietary change with low-income and minority women, and the experiences of this trial will incorporated into the larger trans-NIH initiative.

The National DES Education Program for Health Professionals and the public includes NCI efforts to provide information and recommendations to women exposed to diethylstilbestrol, a drug used during the 1940s and 1950s to prevent miscarriage. Strategies are aimed at informing health care professionals about DES-induced cancer risk for patients and their children. Treatment standards are in development and activities are being implemented to reach patients at risk for DES-induced disease.

The Prostate, Lung, Colorectal and Ovarian Cancer Trial (PLCO), initiated in 1993, is expected to screen 37,000 men for prostate, lung, and colorectal cancer. An equal number of women will also be screened for lung, colorectal, and ovarian cancer in an attempt to determine the impact of screening on disease-specific mortality. One of the anticipated benefits of this study will be the identification of biomarkers indicative of cancer in its earliest stages and intermediate endpoints for future prevention trials.

The Prostate Prevention Trial began in October 1993, in the NCI Community Clinical Oncology Program. This ten-year study of 15,000-20,000 men will test the ability of finasteride (Proscar), a 5-alpha reductase inhibitor of androgen synthesis, to reduce prostate cancer incidence. Finasteride also blocks the production of dihydroxytestosterone and may provide insight into prophylactic intervention in benign prostate hyperplasia. A diagnosis of clinically significant prostate cancer will be the study endpoint.

The Breast Cancer Prevention Trial (BCPT) of tamoxifen is being conducted through the Community Clinical Oncology Program and the National Surgical Adjuvant Breast and Bowel Project. After considerable re-examination of the risk of secondary cancers and issues of study management, this trial is continuing to examine the prophylactic effect of tamoxifen in preventing breast cancer in women at high risk for the disease.

Breakthrough technologies for breast imaging were assessed during 1993 and several proposals to develop a digital detection and display system to generate high contrast, high resolution, high field of view images with high performance, low cost networks were considered. Multidisciplinary teams composed of clinical radiologists, physicists, and technical equipment designers from industry and the private sector will be supported through a collaboration between the NCI and the National Aeronautics and Space Administration.

## B. Cancer Treatment

During 1993, the first human trials of anti-cancer vaccine therapy were initiated as a joint effort between the Division of Cancer Treatment (DCT) and the Division of Cancer Biology, Diagnosis and Centers (DCBDC) using a recombinant construct of vaccinia virus containing a tumor specific antigen called carcinoembryonic antigen (CEA). The Institute has continued preclinical and clinical development of gene therapy as an approach to cancer treatment and in its efforts to identify natural products for use in AIDS. The gene for the Von Hippel-Lindau syndrome (familial renal cancer) was also identified by NCI intramural scientists.

Taxol, a natural product developed as an NCI initiative, was approved by the FDA for treatment of women with refractory ovarian cancer; its use has just been approved for recurrent breast cancer, and its efficacy in the treatment of other malignancies is being studied. Initial Phase I/II studies in



refractory ovarian cancer have revealed significant activity (response rates of 21 to 40 percent) and response rates of 56 to 62 percent in metastatic breast cancer. Using a multi-drug approach, Phase II trials in the Gynecologic Oncology Group, one of the NCI-supported clinical cooperative groups, compared taxol plus cisplatin to standard therapy with cyclophosphamide and cisplatin in patients with suboptimal debulking of ovarian cancer. The experimental treatment arm was associated with significant improvement in clinical response rate and an increased rate of negative, second-look laparotomy. Survival impact has not been fully assessed. Suramin, a prototype heparin-binding polyanionic compound involved in growth regulation was found to have significant impact with few toxicities in metastatic prostate cancer when administered in an outpatient setting. Other new drugs, including the camptothecins, the anthrapyazoles, Taxotere (a Taxol analog), and temozolomide have also entered clinical testing.

Thymidylate synthase (TS), an enzyme important in pyrimidine nucleotide biosynthesis, provides the cell with the only *de novo* source of deoxythymidine monophosphate essential to DNA synthesis. TS is the target enzyme for anti-metabolites of 5-fluorouracil (5-FU) and 5-fluorodeoxyuridine (5-FUdR). TS level increases following 5-FU therapy suggest that TS is an important indicator of sensitivity to the fluoropyrimidine therapy. New antibodies have been developed by DCT researchers for use in detecting and quantitating TS levels and distinguishing free enzyme from enzymes in complex. Research is underway in association with ongoing trials to determine the prognostic significance of baseline levels of TS in patients with colorectal cancer. This is also being examined in relation to the progression of ductal carcinoma *in situ* to invasive breast carcinoma. This work illustrates clearly the translation of basic research into clinical applications that benefit patients.

## C. Cancer Etiology

The Division of Cancer Etiology has embarked on a series of non-human primate studies to determine the level of risk heterocyclic aromatic amines (HAAs) pose for humans and to develop ways to mitigate this risk. HAAs are formed during the normal process of cooking meat, fish, and poultry at high temperatures (e.g., frying, broiling, barbecuing). Their carcinogenicity has been shown in standard bacterial tests and in rodents. One HAA in particular, PhIP, has been shown to induce high percentages of breast and colon cancers in rats. Both the mutagenic effects and the carcinogenic effects of HAAs are caused by their metabolites which react with DNA to form adducts. Examining their potential role in human cancer is therefore critical.

Various genetic alterations have been associated with different forms of cancer, but the most prevalent have been alterations in the p53 tumor suppressor gene. These mutations are thought to cause the loss of normal tumor suppression or cell growth control. Different carcinogens cause specific mutations which are linked to certain cancers. This evidence leads to the hypothesis that various environmentally induced cancers may leave reproducible "fingerprints" through the genetic mutations induced. One rare genetic disorder, the Li-Fraumeni Syndrome (LFS), may be associated with p53 mutations in germ cells, allowing passage of the disease from generation to generation. However, inconsistencies in disease occurrence and presence of the mutations suggest further molecular study of LFS is needed.

Human papillomaviruses (HPVs) have been linked to cervical dysplasia and other pre-neoplastic lesions that may progress to malignancy, and to cervical carcinoma and other anogenital cancers.

Close examination of the viral genes has found that two genes, E6 and E7, are capable of causing cellular transformation through the formation of complexes which affect cell growth regulation.

Finally, the NCI undertook a wide variety of epidemiologic studies of environmental and other exposures and cancer outcomes in women. These focus on malignancy of the breast, ovary, cervix, endometrium, and vagina/vulva. Data from a recently completed large case-control study of the effects of exogenous hormone use (oral contraceptives and menopausal hormone replacement) effects on cancer incidence are now being analyzed. The analysis also will assess differing cancer incidence rates in African American and white women. In addition, a comprehensive analysis of factors leading to excess breast cancer incidence on Long Island has begun. The Long Island Study will combine efforts and resources of numerous agencies and private organizations to examine the multiple environmental, occupational, behavioral, cultural, and socioeconomic factors affecting this population of women.

### D. Tumor Biology and Immunology

In addition to the CEA vaccinia vaccine trial mentioned previously, PSA-vaccinia virus constructs are being used to examine the potential of the prostate specific antigen for immunotherapy of prostate cancer. Permission is currently being sought for clinical trials.

CAI, a novel signal transduction inhibitor that blocks tumor cell cytokine-stimulated growth and motility, has been developed as a new therapy for ovarian and breast cancer. Phase I trials began in 1992 and have shown low toxicity and promising tumor response in some patients. Additional progress has been made in understanding the NM23 gene family role in tumor metastasis regulation. NM23 expression is reduced in highly metastatic human breast, hepatocellular, and melanoma tumors which suggests its potential use to predict tumor aggressiveness. TIMP-2, a protein that inhibits enzymatic breakdown of basement membrane, has been shown experimentally to block metastasis. Both the structure and location of TIMP-2 have been determined and data suggest that it may function as a tumor suppressor protein by inhibiting metalloprotease activity necessary for pre-metastatic cellular invasion. *In vivo* TIMP-2 also affects metastasis by inhibiting angiogenesis. Potential clinical applications of TIMP-2 include treatment of bone metastasis and Kaposi's sarcoma.

A new laboratory assay has been developed for HPV gene products based on detection of HPV16 L1/L2 particles. This may prove to be a useful adjunct to cervical cytologic screening to identify women at high risk for developing cervical cancer. These same L1 and L2 particles appear to be highly immunogenic and may provide the basis for developing a cervical cancer vaccine.

New technologies, comparative genomic hybridization (CGH) and arbitrarily primed polymerase, will make it possible to examine the entire genome for mutations without prior knowledge of location. These new techniques are being applied to rapidly identify genetic alterations involved in cancer initiation and progression. An example of their application is the recent discovery of the gene associated with some hereditary colon cancer.



## III. CONCLUSIONS

An estimated 1,170,000 Americans were diagnosed with cancer in 1993 and approximately 526,000 people died of cancer during that year. Despite significant reductions in mortality for some cancers and improved technologies across the continuum of cancer care, overall survival has improved only modestly since 1973 while incidence and mortality rose alarmingly. Lack of access to early diagnosis and state-of-the-art treatment remains a problem that research alone cannot solve. Many cancers are related to tobacco use and improper diet; responsible public policy and targeted public education can do much to safeguard and empower people to help prevent these cancers. Cancer incidence and outcomes continue, however, to be affected profoundly by poverty, age, race, ethnicity, and culture. The current health care system, with its ever-tightening fiscal constraints, frustrates the provision of optimal cancer care even for the well-insured and threatens the future of cancer research.

The National Cancer Program encompasses not only cancer research, but all public, private, voluntary, and individual activities that impact our national cancer problem. The fruits of research and cancer care delivery advances achieved since passage of the National Cancer Act are seen in hospitals and laboratories around the world, but much remains to be done. Cancer-related research, health care, and public policy in this country currently suffer from a lack of national coordination, which must be addressed to make the most of available resources and most rapidly reduce our people's suffering due to cancer.

Improved early detection and diagnostic techniques and more effective but less toxic cancer treatments must be developed, but improved prevention and control will have the greatest impact on future cancer incidence and mortality in America. To achieve these critical goals, cancer research, interventions, and data collection activities must be conducted in the context of human behavior, embracing and incorporating our population's cultural, economic, ethnic, and educational differences.

The recently completed National Cancer Program evaluation, Cancer At A Crossroads: A Report to the Congress for the People, conducted at the request of Congress by a subcommittee of the National Cancer Advisory Board, has reached conclusions consistent with those of this Panel, and with which we concur fully. Of particular importance, we share the view that basic research provides the knowledge necessary to develop new cancer prevention and care, and that translational research is the crucial bridge between basic and clinical research. Moreover, it must be recognized that the flow of information and ideas must be bi-directional and ongoing, since clinical observations provide important feedback to the basic scientist, and vice versa.

Continuing its role to monitor the National Cancer Program and identify barriers to progress, the Panel heard testimony during 1992 and 1993 and concluded that:

- A strong basic research network must remain the foundation of the National Cancer Program. The vast increases in cancer knowledge and technology achieved during the past ten years have been rooted in basic research. Consistent support for basic research is necessary to exploit unprecedented opportunities that will provide the basis for future cancer prevention and cancer care advances.

- Translational research -- by which basic science discoveries become technologies and therapies ready for clinical trials and possible widespread application -- must receive greater support. Funding mechanisms must be both consistent and sufficiently flexible to allow this fusion of basic and clinical research that will lead to more effective cancer prevention, detection, treatment, and supportive care. In particular, increased support for translational programs should be made available through the NCI-designated Cancer Centers, the Community Clinical Oncology Programs, and the SPORES.

- Improved communication must be fostered between government at all levels, advocates, patients, clinicians, scientists, and industry; improved communication is critical to the cooperative movement of basic science discoveries through testing into application.

  -- Existing systems for collecting epidemiologic and clinical data must be enlarged, standardized, and made more accessible.
  -- Duplication of effort must be avoided to maximize scarce resources.
  -- Intellectual discoveries made by either government or industry investigators must be protected and developed into improved cancer prevention and care in a manner that benefits the public.

- To ensure continued progress against cancer and our world leadership in the development of new cancer knowledge, both the content of our educational programs and the incentives provided for young scientists to accept the challenge of cancer research must be re-examined.

  -- Training must be provided that fosters a new generation of scientists and clinicians who are culturally aware, trained in epidemiologic methods, and prepared to undertake the task of translating bench research into clinical applications.
  -- Funding for this training must be stable.
  -- Cancer research funding must be sufficient to provide young investigators with a reasonable chance of securing support and a reasonable assurance of a viable career in cancer research.

- The major research emphases of the National Cancer Program must shift from diagnosis and treatment to prevention and management.

  -- Continued basic research into biomarkers for prognostic use and as markers of disease progression are required.
  -- Prevention strategies must be culturally sensitive and respect human dignity.
  -- A comprehensive school health education program under the leadership of the Department of Education may make better use of limited funding compared to targeted options that may have limited or less enduring impact.



- People with cancer and those at risk are both the beginning and the endpoint of successful cancer research; cancer researchers must remember that the individual cannot be isolated from his or her surroundings.

  -- Socioeconomic, cultural, and ethnic biases affect access to education, preventive health care, treatment, and the individual's ability to follow required treatment regimens.
  -- Attention must be paid not only to research objectives, but to quality of life issues relative to preventive interventions, cancer detection methods, treatment, and supportive and palliative care.
  -- Psychosocial aspects of cancer must be more thoroughly researched and supported; such research may require the inclusion of non-traditional disciplines such as sociology, ethnography, behavioral psychology, or anthropology.


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