February 1, 1994 to December 31, 1995

President's Cancer Panel

Report of the Chairman

PRESIDENT'S CANCER PANEL
National Cancer Program

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NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

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

Dear Mr. President:

By the year 2000, cancer is expected to surpass heart disease as the leading cause of death in the United States. Four in ten Americans will develop cancer in his or her lifetime. In the coming year, over a million of our people will be diagnosed with cancer, and the disease will take more than a half million from their loved ones. The estimated annual cost of cancer to the United States, excluding incalculable psychosocial costs, approached $100 billion in 1990.

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 and barriers to its progress against the more than 100 diseases we call cancer. I was appointed to the Panel in 1991 and currently serve as a member and Chairman. Ms. Frances M. Visco, Esquire was appointed to the Panel in 1993 and will serve until May 1999. Dr. Henry Pitot completed his appointment to the Panel in May 1995 and was replaced by Dr. Paul Calabresi, who will serve as a member until 1998. On behalf of the Panel, I respectfully submit the attached report covering 1994 and 1995.

In previous communications to your office, the Panel has emphasized a fundamental goal that we, as members of the Federal Government, must achieve if we are to reduce the cancer burden on the nation. That goal is educating and empowering the people to protect their own health status. Many causes of cancer are avoidable. Each American must recognize and choose health-promoting behaviors over those that jeopardize health, and seek appropriate preventive and curative treatments as needed throughout life.

There are, however, significant barriers to achieving this goal and thereby reducing the suffering caused by cancer. Access to appropriate preventive, diagnostic, and definitive cancer care continues to be limited in many poor and culturally diverse segments of the population. As a result, these Americans often are diagnosed with more advanced cancers and have lower survival rates. Those at high risk for cancer fail to receive essential screening and surveillance. Even when access to care is possible, coverage for health care costs remains out of reach for millions of our people who are unemployed, work at part-time jobs that lack health benefits, or have pre-existing conditions, including cancer, that render them uninsurable.

I believe firmly and have continually stressed in my role as Chairman of the Panel 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. As we approach the 25th anniversary of President's Nixon's declaration of war on cancer, we must leverage our extraordinary victories of vastly expanded knowledge about how normal cells become cancer cells and our progress against childhood and other cancers to more fully apply what we now know to improvements across the continuum of cancer care--prevention, detection, diagnosis, treatment, rehabilitation, and palliative care--for all of the population. Despite our successes, cancer remains a tenacious adversary, and much remains to be done.

Recognizing the persistent barriers to the ultimate success of the National Cancer Program, the Panel has, since my last report to you, examined the current level of understanding of avoidable causes of cancer and strategies for transferring this knowledge to the public. In particular, the Panel considered how the varied cultures of America act as prisms through which this information may be viewed, and how culture affects individuals' motivations to seek care and their interactions with the health care system.

The Panel also reviewed current clinical, societal and governmental challenges related to lung cancer, which accounts for 30 percent of cancer deaths each year. An ad hoc committee of the Panel was convened to review the FTC Test Method for determining tar, nicotine, and carbon monoxide levels in cigarettes, and to evaluate the availability and usefulness of test results to consumers.

Other areas explored by the Panel in 1995 included implications of the Human Genome Project for cancer patients and cancer research, and malignancies that are highly prevalent among HIV-infected individuals, severely diminishing both the duration and quality of their lives. The Panel also reviewed progress against leukemia and considered the potential of the expanding information superhighway to advance both technological aspects of cancer care and communications and the social marketing of public health messages about cancer and behavior.

Recurrent themes throughout all these meetings have been the need to more rapidly move basic science discoveries from the laboratory to practical preventive and therapeutic applications for people, and the need to maintain support for basic and applied research to capitalize on existing knowledge and continue the flow of new scientific knowledge which is the basis for improved cancer care. Speakers from diverse disciplines also emphasized repeatedly that research and interventions of all types must recognize and accommodate the cultural, genetic, biologic, socioeconomic, and environmental diversity of our population.

It has also become abundantly clear that the National Cancer Program must address immediately one issue that spans the breadth of cancer research and its translation into routine preventive and medical care: the use--and potential misuse--of knowledge we have already gained in the first 25 years of the Program. Therefore I recommend that the goals of the National Cancer Program should include:

- Strengthening data collection, data sharing, and data protection in the systems that form the information infrastructure of the NCP. Better coordination, standardization, quality control, and data protection are needed as information technologies--supporting research and insurance evaluation of populations--continue to develop at a breakneck pace. Improved information sharing also means ensuring that all Americans have complete, truthful, and understandable information about health risks (e.g., smoking) and the need for various dietary constituents. Moreover, researchers and physicians must embrace the evolving relationship with more knowledgeable consumer-patients.

- Developing and implementing a national curriculum, beginning in the primary grades and continuing throughout the school years, that fosters health promoting behaviors and nurtures personal responsibility for maintaining a healthy lifestyle.

- Ensuring that health professionals and researchers are educated to make maximum use of exploding information resources and technologies, including improved data collection abilities needed to support research and optimal patient care, and skills needed to navigate current and future information resources for basic, clinical, and population-based research.

- Enhancing public and private support for and participation in clinical research, particularly translational research. Clinical research makes an irreplaceable contribution to reducing the staggering cancer burden and its associated economic and social costs. Managed care systems and other public and private sector constituencies must participate more fully in clinical research. The public must better understand that clinical research benefits all Americans. We must provide appropriate incentives to attract and retain talented and creative investigators in cancer research.

- Carefully considering ethical, legal, social, economic, and privacy concerns associated with emerging genetic and related technologies and their impact on the individual. It is critical that genetic testing is limited to the research arena until the economic and psychosocial impact of test results is understood. Personal genetic information must be closely guarded; it must not become a basis for employment or insurance discrimination.

I and the other members of the President's Cancer Panel are privileged to assist you 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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INTRODUCTION

Forty percent of the American public will develop cancer in their lifetimes; 20 percent will die of their disease. Some 1.25 million new cases of cancer will be diagnosed this year, and ten million Americans are already living with a diagnosis of cancer. Although 50 percent of those diagnosed with cancer can expect to live for five years or more, inadequately addressed psychosocial and functional issues compromise the quality of their lives.

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.

The 1971 National Cancer Act codified the recognition that cancer research advances would derive from a broadly based effort. It charged the National Cancer Institute (NCI) Director to coordinate "all the activities of the National Institutes of Health relating to cancer with the National Cancer Program" and "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 importance of this charge grows with every passing year. In the 25 years since passage of the National Cancer Act, our grasp of the nature of cancer--how a normal cell becomes a cancer cell--and of the nature of life itself has grown beyond all expectations. So too have we learned that every facet of society and every individual are key players in the National Cancer Program.

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.

Without question, significant advances have been made in basic, clinical, and applied cancer research; and there is vast potential to more fully apply these advances to reduce cancer-related illness and death and improve survival and quality of life for the cancer patient and family. 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 that the age-adjusted rate of increase in deaths due to

cancer from 1973 to 1993 is approximately six percent (National Center for Health Statistics data). This age-adjusted rate accounts for both population increases and the shift to older ages.

According to Surveillance, Epidemiology, and End Results Program (SEER) data, cancer incidence has increased by approximately 27.3 percent from 1973 to 1993, while survival has increased by only eight percent during roughly the same period. And although these figures largely reflect improvements in detection of breast and prostate cancer, six cancers appear to be responsible for 68 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 all SEER data-based.]

Since 1971, improved surgical techniques and refinements in chemotherapy and radiotherapy have afforded many patients the chance to fight their disease with less radical or invasive surgical procedures and non-surgical options that spare organs and limbs, control treatment side effects and cancer-related pain, and preserve self-determination and personal dignity. With astonishing advances in molecular medicine, genetics, and epidemiology, we have arrived at a new era in cancer research and cancer care that will bring to the people even greater benefits through prevention and early detection in the coming decades.

The President's Cancer Panel, consisting of myself as Chairman, Dr. Henry Pitot of Madison, Wisconsin, and Ms. Frances Visco, Esquire, of Philadelphia, Pennsylvania, began our consideration of the issues identified above in 1994; Dr. Pitot was replaced by Dr. Paul Calabresi, of Providence, Rhode Island in May 1995.

I. MEETINGS OF THE PRESIDENT'S CANCER PANEL

The Panel held four meetings in 1994; our report on the first of these, "The Role of Government in the Research Mission of the National Cancer Program," was included in our most recent previous report on Panel activities from January 1, 1992 to January 31, 1994, and will not be discussed here. The sections below summarize key findings from the remaining three 1994 Panel meetings, and the four meetings held in 1995.

A. Avoidable Causes of Cancer

It is believed that a high percentage of cancer incidence in the United States is attributable in part to lifestyle factors and environmental and occupational exposures that may be avoidable. The Panel met on April 7, 1994 in Bethesda, Maryland to define "avoidable" as applied to cancer, examine predisposing factors for cancer, consider research opportunities in cancer etiology and prevention, and determine how existing scientific evidence can be translated into public policy. In this regard, the Panel heard testimony from representatives of the National Cancer Institute and other Federal agencies, and from panels of experts in epidemiologic and basic research, medicine, and social work in the areas of tobacco, alcohol, diet and nutrition, hormones and

medication, occupational and environmental exposures, radiation, infectious agents, and susceptibilities related to gender, ethnicity, and genetics.

Nicotine addiction is arguably the most common serious medical challenge in the United States and the chief cause of avoidable morbidity and mortality. Tobacco use is responsible for over 30 percent of American cancer deaths and over 90 percent of lung cancers. Speakers reviewed tobacco research and smoking trends by age groups, gender, and ethnicity. Greater attention must be paid to educating children and youth about the health risks of tobacco use, since few people initiate smoking after the teen years. Speakers noted that the doctor-patient relationship can be a powerful tool for motivating smokers to quit and emphasized the need for policy changes that limit tobacco access among youth, protect nonsmokers from environmental tobacco smoke, regulate tobacco advertising and promotion, and support innovative biobehavioral tobacco control research.

Speakers reviewed alcohol research of the last four decade which has shown that alcohol consumption is clearly associated with cancers of the upper digestive tract and oral cavity. More research is required to determine conclusively if there is a causal relationship between drinking and either breast or colorectal cancer. The panelists also indicated a need to explore further the carcinogenic mechanisms of alcohol, its synergy with smoke and other carcinogens, and relative risks associated with beverages of varying alcohol concentrations and with quantity consumed. Cancer risk associated with moderate alcohol consumption is of particular interest.

A panel addressing the area of diet/nutrition and cancer summarized the evidence to date indicating that approximately 35 percent of cancer mortality in the U.S. may be attributable to dietary factors, with a range for different cancer sites of from 10 to 70 percent. These statistics point to the need for an intensive nutritional research science program that focuses on clearly elucidating diet-cancer risk relationships and the mechanisms by which dietary elements either protect against cancer or increase risk. Such a program should include basic science, epidemiology, clinical trials, and follow-up to transform hypotheses into established truths people can use to select foods that will reduce their risk of cancer. Current evidence indicates that the most important dietary changes Americans can make today are to eat more fruits and vegetables and less red meat. The speakers identified critical needs for improved dietary assessment instruments, increased funding for nutritional research (currently five percent of NCI-sponsored research funding), and incentives to attract students to nutritional science, particularly the study of nutrition in cancer etiology and prevention. Finally, these speakers stressed the need for culturally appropriate nutrition prevention and intervention efforts.

Elucidating the long-term effects of medications on cancer risk is difficult because of limited exposures, long latency periods, and the small relative risk associated with medications. Cancer risks associated with radiopharmaceuticals, immunosuppressive and antimetabolite agents, arsenic and coal tar agents, alkylating agents, and various exogenous hormones have been described extensively. More attention is needed to the possible cancer risks associated with ovulation-inducing drugs and certain widely used prescription and over-the-counter medications, and to testicular cancer risks of sons of

women exposed to diethylstilbestrol (DES). Women need to be fully apprised of risks associated with estrogen replacement therapy (ERT) and the dual cancer risks and protective effects of hormonal contraceptives. New strategies are needed to minimize the negative effects of lifetime estrogen exposure (e.g., higher breast and endometrial cancer risks), while preserving its protection against osteoporosis and cardiovascular disease. Translational research, bridging basic and clinical investigation, will be essential to synthesize knowledge from varied disciplines and develop preventive strategies for hormone-linked cancers.

Occupational studies are important because high incidence cancers and several carcinogens were first identified in workplace settings, and the workplace provides a more controlled environment to intervene and prevent certain cancers. Moreover, minorities and members of lower socioeconomic groups are disproportionately affected by some occupational exposures. Speakers reviewed existing evidence on exposures particular to various occupational settings, emphasizing cancers with increased incidence among farmers and their families, and the pressing need for information on occupational exposures among female and minority workers. General environmental exposures, such as air and water pollutants that may increase cancer risk, were also discussed. Speakers in both of these areas pointed out barriers posed by currently inadequate tools and protocols for assessing occupational and environmental exposures. It was suggested that existing cancer registries could be expanded in scope to collect information on these exposures and thereby become a more effective tool in prevention research.

While there is no question about the cancer-causing potential of ionizing radiation, more research is needed on low-level (nonionizing) radiation exposures, such as those from microwave ovens and cellular telephones. Speakers indicated that additional research is needed on the risks of environmental radon exposure, particularly in the home. Standards for residential radon control will need to take into account the demonstrated interactions between smoking, radon exposure, and cancer. Concerning ultraviolet radiation, speakers reviewed current incidence and mortality rates for melanoma and nonmelanoma skin cancers and outlined existing primary and secondary prevention strategies. The speakers in this area agreed that the effects of exposure to electromagnetic fields remain highly controversial and require further epidemiologic and laboratory research.

A number of infectious agents are implicated in human cancers. Speakers reviewed what is known about viral agents and related cancers including hepatitis B and C and liver cancer; human T-cell lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/-lymphoma; Epstein-Barr virus and Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgin's disease; and human papillomavirus (HPV) and cervical cancers. It was noted, however, that the majority of people carry these oncogenic infections without developing malignancy; cancer risk appears to be related to mode of infection or immune suppression. Although many bacteria are suspected causes of cancer, none have been confirmed. Speakers noted, however, that bacteria, unlike viruses, are treatable with antibiotics, suggesting that bacteria-induced cancers are preventable. *Helicobacter pylori*, a highly prevalent pathogen linked to gastric cancers, may offer the best existing model for preventing and treating bacterially-induced cancers. Speakers also urged expansion of

vaccine research to combat virally-linked cancers and the inclusion of anthropologists on teams exploring cancer etiologies and mechanisms.

A recurring theme of the meeting was the interaction of ethnicity, environment, gender, and cancer. A panel of speakers addressing this area in detail emphasized that almost every phase of the multistage process of carcinogenesis may be modified by inter-individual susceptibility resulting from gender, race, and ethnicity. Other factors that increase cancer risk among ethnic and minority group members include lower educational levels, higher unemployment levels, lower socioeconomic status, urban lifestyles, higher exposure to occupational carcinogens, high stress levels, and poverty. In addition, dietary and environmental changes accompanying migration have been shown to modify risk for some cancers. The speakers also emphasized that an overwhelming majority of etiologic research, particularly concerning occupational exposures, has been limited to studies of white men; as a result, we know little about gender, racial, and ethnic differences in cancer risk related to these potentially avoidable exposures in women and minorities. There is also a need for models to help determine whether gender, racial, or ethnic cancer risk variations, even within subgroups of each population, are a result of differences in exposure or biological response due to inherited or environmentally-induced genetic predisposition, or to metabolic factors.

B. Lung Cancer: Clinical, Societal, and Governmental Challenges

In October 1994, the Panel met to examine "Lung Cancer: Clinical, Societal, and Governmental Challenges." Lung cancer may be the greatest unacknowledged cancer disease in this country; approximately 150,000 new cases are diagnosed annually, and 27 percent of the adult population indulges in smoking, the most avoidable cause of lung cancer. Because lung cancer is a chronic disease process with a latency period of 20 years or more, people need to overcome the notion that they are "healthy" until they develop cancer.

Seventeen speakers reviewed current basic science knowledge about lung cancer, described mechanisms of induction and progression, and outlined treatment interventions in use and under development. Although survival improvements have been realized for certain subpopulations of lung cancer patients, overall survival from the disease remains a disappointing 13 percent at five years. Currently, chemotherapy is the most effective treatment for small cell lung cancer (SCLC). Surgical resection is most effective for non-small cell lung cancer (NSCLC), although recurrence of distant metastases or second primary lung cancers are major impediments to the prolonged survival of these patients.

Recent achievements in molecular biology and lung cancer genetics are opening new gateways to progress against this malignancy. These include identifying p53 mutations in approximately 80 percent of small cell lung cancers (over 95 percent of SCLC is smoking-linked) and pinpointing the location of G to T mutations that activate ras proto-oncogenes in many lung cancers. It is increasingly recognized that individuals' genetic risk, including susceptibility and ability to metabolize carcinogens, may be more important than level of exposure and may vary considerably by race, gender, ethnicity, and individual.

Among the early detection techniques under investigation is the use of sputum samples to detect epithelial abnormalities at a much earlier point than is possible with serum methods. Chemoprevention studies suggest that retinoids may suppress primary invasion and reduce second primary tumor development in some patients. Researchers are targeting chemopreventive efforts toward former smokers since it appears chemopreventive agents may be more effective in the absence of ongoing carcinogen exposure and because former smokers may have better motivation and compliance. However, barriers to research and development of chemopreventive agents include lengthy clinical trials driven by long latency periods in lung cancer, inadequate patent protections, and pharmaceutical companies' liability exposure.

Focusing on sociocultural differences that influence smoking behavior, speakers suggested that Latino smoking patterns are highly influenced by level of acculturation. Smoking patterns among African-Americans are strongly influenced by tobacco industry marketing, stress due to socioeconomic circumstances, and lack of social support. A notable exception is the low rate of smoking among African American teenagers; studies were urged to learn why these youth are choosing not to smoke and how other youth populations can be similarly motivated.

Among Native Americans, who have the lowest lung cancer survival rates, it appears that culture exerts a greater influence on smoking habits than either education or income level, and intervention effectiveness has been limited by the wide diversity of customs and beliefs in this population. Blue collar workers are disproportionately burdened by lung cancer because of exposure to occupational carcinogens that may act synergistically with carcinogens in tobacco smoke. It was suggested that SEER, other cancer registries, and other national data collection efforts should collect more detailed data on cultural variables and occupational environments.

Presenters stressed that new knowledge does not immediately translate into new interventions or treatment. To reduce lung cancer mortality, scientists and the public must focus on cancer prevention and control, and more rapidly apply what we already know. To accelerate the process of translating basic discoveries into clinical investigations and treatment advances in lung cancer, NCI funds two Specialized Programs of Research Excellence (SPOREs), at Johns Hopkins University and at the University of Colorado.

Speakers also reviewed activities and barriers to legal and regulatory actions to limit the availability of tobacco to youth, to limit exposure to environmental tobacco smoke, and to hold tobacco companies responsible for the harms and related societal costs (e.g., increased Medicaid costs) they cause. By labeling smoking as a pediatric disease and linking tobacco addiction to numerous chronic health problems, public attention may be focused on the issue and the tobacco industry assertion--that government agencies have no appropriate role in tobacco control because smoking is a matter of choice--may be discredited. Since it is more difficult for the tobacco industry to lobby against local ordinances than state and Federal laws, tobacco control advocates are working to promote local laws and prevent preemption clauses in state legislation. Barriers to better collaboration between Federal agencies on cancer issues include the limitations of

each agency's purview and the need of each agency to focus on fulfilling its specific mission.

In addition to this meeting addressing the continuing challenges in lung cancer prevention and treatment, an ad hoc committee was convened under the auspices of the Panel to review and make recommendations on the Federal Trade Commission (FTC) Test method for determining tar, nicotine, and carbon monoxide levels in cigarettes. The Committee concluded that the smoking of cigarettes with lower machine-measured yields has a small effect in reducing cancers caused by smoking, no effect on cardiovascular disease risk, and an uncertain effect on pulmonary disease risk. A reduction in machine-measured tar yield from 15 mg. tar to 1 mg. tar does not reduce relative risk from 15 to 1. Moreover, the FTC test protocol does not take into account the wide variations in human smoking behaviors.

The Committee made several recommendations, among them that information on the range of tar, nicotine, and carbon monoxide yields likely from each cigarette brand (including generics) should be measured and communicated clearly to the public using a simple graphic representation that does not imply a one-to-one relationship between measurements and disease risk. To avoid confusion, the Committee recommended that no smoke constituents other than tar, nicotine, and carbon monoxide be measured and published at this time, although cigarette packaging and advertisements should inform smokers of the presence and toxic effects of other smoke constituents. In addition, the Committee recommended that the system be evaluated every five years to ensure its continued utility to smokers, and continued Federal agency oversight of the testing process and involvement in the complex medical and scientific issues related to the FTC test protocol.

C. Cancer and the Cultures of America

The final Panel of 1994, held in San Francisco, California, explored "Cancer and the Cultures of America." Twenty-six speakers reviewed cultural influences that may affect cancer risk, survival, and mortality among the many diverse populations of the nation.

Speakers emphasized the importance of recognizing differences in perceptions of health and illness, other attitudes, beliefs, and practices both between and within population groups. Significant attitudinal, acculturation, and behavioral differences exist within the African American population; among Cuban, Mexican, Puerto Rican, and South American Latino populations; among Chinese, Japanese, Korean, and Vietnamese Asian populations; among Appalachian populations from the different states in that region; and among the highly diverse Native American populations (e.g., Samoan, Native Alaskan, Native Hawaiian, Filipino, American Indian tribes). Important cultural and behavioral differences also exist within subgroups of the gay and lesbian populations, and between religiously-defined populations (e.g., Latter Day Saints and Seventh Day Adventist) that have similar values and practices.

Presenters suggested that studies of geographically isolated or otherwise relatively sequestered cultures may provide unique opportunities to study specific cancers. For

example, some Plains Indians families have an unusually high incidence of kidney cancer, which has a high incidence in very few other populations. Caucasian members of the Latter Day Saints (LDS) and Seventh Day Adventists, whose religions prohibit smoking or alcohol use and promote low fat diets, early childbirth, and large families, have significantly lower rates of many cancers than the general population. A study of African American Seventh Day Adventists will investigate whether this population experiences cancer rates similar to white Seventh Day Adventists. It was also suggested that a comparative study of cancer incidence and mortality among individuals belonging to the Nation of Islam could likewise help elucidate the effects of genetic versus behavioral differences, since this religious group adheres to behavioral proscriptions similar to LDS members and Adventists, but includes large numbers of members from differing ethnic and racial groups.

Barriers to providing cancer screening, diagnostic, and treatment services to people with other than mainstream cultures include distrust of the health care system, reliance on traditional healers, tendency to avoid seeking care until illness disrupts daily activities, fatalism concerning cancer, unawareness of cancer as a personal health concern, limited access to care, and lower language and literacy skills that limit information transfer and affect the doctor-patient relationship.

Revisiting issues explored at the Panel's June 1992 meeting, "Cancer in Minority Populations: Opportunities and Obstacles," speakers repeatedly underscored that researchers and those developing interventions need to understand and accommodate cultural differences if they hope to succeed in reducing cancer burden in these populations. This includes involving community members in research project and intervention planning, understanding how group members prefer to receive and transmit information (e.g., story telling traditions of Native Americans) and involving group members as community liaisons or in other roles. In addition, speakers emphasized the contributions to be made by ethnographers, sociologists, and anthropologists who can provide knowledge about actual rather than assumed beliefs and practices of various populations that impinge on health behaviors, and help researchers and health providers better understand culture (including the culture of poverty) as a learned response to a group's environment.

D. The Human Genome Project and Disease Prediction

The first Panel meeting of 1995 was held on March 28 in Bethesda, Maryland to examine the potential research benefits of the Human Genome Project for advancing knowledge about cancer etiology, risk, and treatment; and the clinical, ethical, and personal implications of genetic research for cancer patients and those found to be at risk for cancer.

The 15-year Project involves a three-phase process: locating genetic markers for specific genes and developing a genetic map; cloning DNA segments and isolating target genes; and the culminating challenge of sequencing the entire human genome. The Project is also exploring the ethical, legal, and social ramifications of human genetic knowledge, including (1) developing strategies to promote the responsible use of genetic information,

particularly in regard to presymptomatic cancer testing and health insurance guidelines for patients with genetic predispositions; (2) developing model legislative language and procedures for ensuring the privacy and appropriate use of genetic information; and (3) educating the public and health care professionals through television programming, other educational mechanisms, and public forums in which the implications of genetic information for society as a whole and for cancer patients as individuals can be discussed.

Speakers described the identification of nearly 20 regions of the human genome where mutation (loss of heterozygosity) occurs in primary human breast tumors, the sequencing of chromosome 17q clones containing the BRCA1 locus, and the use of mutational spectrum analysis to study the etiology of cancers linked to environmental exposures and to develop indicators of racial and gender differences in cancer incidence, particularly lung cancer. *VHL*, a gene identified for the familial kidney cancer associated with Von Hippel-Lindau disease and also associated with the nonfamilial, more common form of clear-cell kidney cancer, also provides unique opportunities to evaluate the relative contribution of environmental factors in sporadic kidney cancers versus the inherited germ line mutations seen in the familial form of the disease.

Several barriers inhibit the application of newly acquired knowledge from genetic research to the development of better therapies, particularly new drug therapies. Industry is positioned to utilize knowledge of gene targets and gene sequences for drug design, but the process is costly and, as in all drug development, the probability of developing a successful drug is low. In addition, commercial patent protection concerns compete with the need to make gene sequences freely available to stimulate further research. Public/private research partnerships have created a dilemma concerning the ownership of genetic tests and potential access by the American public.

The Human Genome Project has helped to develop guidelines and support research in genetic risk assessment and counseling. Counseling for genetic risk has evolved into a multidisciplinary team approach necessary to explain complex information about genetic risk for specific cancers diseases and other diseases, to relate this information to family history and other personal data, to recommend disease prevention and early detection practices for the individuals in the family, and to provide psychological counseling when necessary. The need to train health professionals to provide this complex counseling support was emphasized.

A major focus of the meeting was the legal and ethical aspects of genetic research and testing, and how genetic information may affect individuals' access to health insurance. Panel members and speakers underscored the importance of tempering excitement about advances afforded by this research with early and careful consideration of the ethical and moral obligations inherent in such developments. Informed consent, privacy, and confidentiality standards and guidelines are needed to protect tissue sample providers from insurance discrimination based on identified genetic predispositions to cancer. The critical need for policy related to these issues was punctuated by the presentation of the experiences of guest speakers who were cancer patients within families exhibiting unusually high cancer incidence and mortality.

E. AIDS Neoplasms

The Panel met again in Bethesda on June 6, 1995 to explore the impact of AIDS in all of its manifestations on the mission and goals of the National Cancer Program. The meeting focused on malignancies that have an especially devastating impact on both the duration and quality of life of HIV-infected individuals, including lymphomas and anogenital malignancies. Epidemiologic studies show that HIV-associated malignancy incidence is influenced by both gender and racial factors, with young minority females exhibiting highest susceptibility. The most prevalent HIV-associated malignancies are Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL). The NCI funds collaborative translational research on HIV-associated cancers through the Multi-State AIDS Cancer Match Registry which uses molecular epidemiologic techniques to detect markers that will indicate susceptibility to malignancies, the Tissue and Biological Fluid Bank, the AIDS Malignancy Consortium, and cancer center programs that target AIDS malignancies.

Speakers, including researchers and a treatment advocacy group, described advances in standard treatment protocols and investigational treatment opportunities in HIV-linked malignancies. The clinical aspects and psychosocial complications (both to the patients and AIDS oncologists who treat them) associated with treatment of HIV-infected patients with malignancies such as KS, NHL, and primary central nervous system lymphoma were also discussed. Therapeutic approaches must include treatment of the underlying HIV disease and prophylaxis of opportunistic infections to counteract the immunosuppressed state of the patients, as well as treatment for the specific cancer disease. Patients should be referred to an AIDS oncologist and the possibility of using novel approaches to treating AIDS-related malignancies through clinical trials should be explored with the patient.

The relationship of HIV infection in women to higher rates and severity of cervical neoplasia was discussed. Cervical cancer is almost always caused by the human papillomavirus (HPV), a sexually transmitted agent, and it appears that molecular interactions of HIV and HPV may result in mutual activation of the two viruses. More study of the interaction of HIV and HPV is necessary, and speakers recommended substantive work be done to develop an HPV vaccine. Similarly, there appears to be at least a temporal relationship between the development of anal intraepithelial neoplasia (AIN), a precancerous lesion, to anal cancer, and the immunosuppression associated with AIDS in HIV-positive men. Anal cancer is one of the most common cancers found in HIV-infected men.

Unusual and unique cancers being seen in HIV-infected children were discussed. Incidence of malignancies such as NHL and other lymphomas is pronouncedly higher among HIV-infected children than among uninfected, immunocompetent children, and HIV-positive children are showing a rising incidence of leiomyoma and leiomyosarcomas, which occur rarely in children. It is believed that growth factors may influence the development of these cancers in HIV-infected children. Though it is too early to fully assess the response of these children to cancer therapy, short, intensive chemotherapy

regimens that limit myelosuppression and avoid cardio- and neurotoxicity have had high response rates.

Findings and recommendations of the Bishop/Calabresi report evaluating the intramural program of the NCI were reviewed. The critical contributions of NCI's AIDS programs in pathogenesis, drug discovery and development, pediatric research, antiretroviral and anti-KS treatments, vaccine research, and epidemiology were recognized.

F. Progress in Leukemia

On July 20, 1995, the Panel met in Chicago to examine current treatment strategies, new research developments, and unmet needs in efforts to treat and cure the various forms of leukemia. Meeting participants included national experts in leukemia research and treatment, and representatives of the NCI, the Leukemia Society of America, and the American Society of Hematology.

Fostering leukemia research is important to continue the considerable progress against these diseases, particularly in pediatric populations, and because leukemia research provides insights and knowledge that can be applied to therapeutic techniques for other adult and childhood cancers. Speakers traced the history of key advances in leukemia treatment: more precise definitions of "remission" and "relapse," differentiation of the two primary forms of acute leukemia, and increased knowledge regarding drug dosage, phasing, and combination. The progress and challenges involved in developing more effective treatments for childhood and adult leukemias were discussed. More support for and access to clinical trials, particularly for children and for the elderly, were cited as key needs to be met. There was a repeated call for the NCI to underwrite these trials since health insurance companies are not allocating money for applied research. It was pointed out that many of the drugs that are evidencing high rates of success would not be available today if not for government-sponsored drug development efforts.

Several speakers addressed bone marrow transplantation and gene therapy issues. Advances in bone marrow transplantation include improved therapeutic techniques that reduce the incidence of graft-versus-host (GVH) disease, greater long-term disease-free survival for adult leukemia patients, and advances in overcoming the host's immune system to permit engraftment of the donor's hematopoietic system. Speakers also addressed requirements to achieve successful gene transfer into hematopoietic stem cells, and discussed benefits of bone marrow transplantation and/or gene therapy alone or in combination. Research needs include critical stem cell research and better methods for purging autologous bone marrow.

Other presentations focused on challenges in treating patients with chronic myelogenous leukemia (CML), adult T-cell leukemia (ATL), acute myelogenous leukemia (AML), and acute promyelocytic leukemia (APL). The pathogenesis of, and current therapeutic practices for, multiple myeloma were also presented and discussed.

Current knowledge and research questions in the study of secondary leukemias--devastating diseases that may emerge as a result of multiagent cytotoxic therapies and

alkylating agents used in cancer chemotherapy--were discussed. Results of chromosomal studies of translocations and deletions and their application to the etiology of secondary leukemias were presented, and the need to closely monitor patients receiving high cumulative chemotherapy doses was emphasized.

The meeting concluded with a discussion of issues involved in recruiting minorities into clinical trials.

G. The Information Superhighway: What Does It Mean For Cancer?

The Panel's final meeting in 1995 was held on September 15 in Baltimore, Maryland, and focused on technological developments affecting medical practice and health communications, and the social marketing aspects of public health information dissemination.

Technological innovations are enabling the collection and electronic transmission of patient data to and from a much wider range of sites, but as these systems develop, care must be taken to protect patient confidentiality and privacy and ensure data quality. The accelerating growth of medical informatics, telemedicine, and distance learning dictates that such safeguards be implemented promptly. Speakers described current programs in teleradiology, telepathology, and telepsychiatry, and distance learning innovations in medical and nursing education. These programs allow patients in remote and rural areas access to expertise at academic health centers and enable health care providers to stay abreast of medical advances. It is also hoped that these technological innovations will assist the national effort to improve retention of health care providers in medically underserved areas.

The potential and challenges in using the Internet as a public health tool were discussed. Public health uses of the Internet include support of international research, electronic communication of health information for consumers and health professionals, and as a mechanism for social support. As speakers pointed out, however, the current user population tends to be concentrated in the upper socioeconomic and educational echelons, the data that can be transmitted over telephone lines is limited, and there is little control over the content of online information. In addition, use of the system is relatively complex, and the lack of security standards precludes physicians from using it to send patient-specific data. There is also a growing need to teach both practicing health professionals and those in training to access and navigate the new information pathways; some medical schools are now including informatics education as a first-year requirement.

Although technological developments such as the Internet present a new panoply of health education opportunities, the information needs of underprivileged Americans who may not even have telephones, and rural and urban physicians who lack Internet access cannot be forgotten. The NCI's International Cancer Information Center (ICIC) and Office of Cancer Communications offer a growing choice of sources through which health care professionals, researchers, and the public can access cancer information, but

will continue to ensure that information is available in hard copy targeted to a range of literacy levels.

Several presentations addressed the marketing of health messages and the effect of communication interventions in shaping health behaviors. It was emphasized that public communications programs that appear to favorably affect health behavior activate a complex process of change in social norms, rather than simply transferring knowledge that produces behavior change. Target markets for health messages should be based on the attitudes and values of people who share a problem; these individualized concerns frequently cut across racial, ethnic, religious, and socioeconomic lines.

II. NCI ACTIVITIES

A. Cancer Prevention and Detection

Chemoprevention Research

NCI-sponsored research in chemoprevention encompasses laboratory and clinical studies of chemopreventive agents, epidemiologic studies, and chemoprevention trials. These distinct areas of research provide for the systematic progression from basic laboratory research to clinical trials and then application to the general public. A highly diverse group of biological and chemical agents that have demonstrated anticarcinogenic activity are currently under investigation. Approximately 27 agents are undergoing clinical testing, and over 400 agents are in the preclinical testing phase. A new clinical program for Phase II trials was initiated during 1994 to accelerate early-stage agent development and strengthen the rationale for chemoprevention trials. The Institute has developed a new initiative to foster research involving the interactions of chemopreventive agents and their modulation of genes and gene products. In addition, Interactive Research and Development projects in chemoprevention continue to facilitate collaborative preclinical and clinical interactions examining the role of biomarkers in assessing risk or modulation by chemopreventive agents.

Several major chemoprevention trials currently in progress include the Women's Health Study, which is testing beta-carotene, vitamin E, and aspirin for the prevention of several cancers (breast, lung, colon) and cardiovascular disease. This trial involves 41,600 postmenopausal health professional women 45 years of age and older. The Breast Cancer Prevention Trial is testing the ability of tamoxifen, an anti-estrogen, to prevent the development of breast cancer in women at increased risk for developing the disease. As of September 1995, over 11,000 of the target number of 16,000 women at increased risk for breast cancer due to age, family history, and personal history have been randomized to receive tamoxifen or a placebo for an initial period of five years. The Prostate Cancer Prevention Trial of finasteride will test the hypothesis that reduction of dihydrotestosterone, a significant androgen in prostate biology, will prevent the development of prostate cancer. The trial will involve 18,000 men over 55 years of age. Subjects are randomized to receive finasteride or a placebo for up to ten years. As of

June 1995, more than 15,000 men have been randomized after a preliminary "run-in" evaluation.

Recent accomplishments also include the completion of two population-based studies showing a positive effect of nutritional supplements on cancer rates in north central China and the recently completed Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study among male smokers in Finland. The results indicated no reduction in the number of lung cancer cases diagnosed or in the total number of deaths that occurred in men who took vitamin E. Followup and ongoing data analysis continues on these studies and others including the National Health and Nutrition Examination Survey (NHANES), the Breast Cancer Detection and Demonstration Project, and cancer-related nutritional information from the Framingham Heart Study.

Tobacco Use Prevention Research

As results began to emerge from NCI's vast tobacco-related research effort of the late 1980s and early 1990s, the Institute systematically collected the findings to help plan a national demonstration project that would document the effectiveness of anti-smoking strategies and contribute significantly to a national reduction in tobacco use before the end of the decade. This project, ASSIST (the American Stop Smoking Intervention Study), is the final phase of the cancer prevention research plan outlined in the early 1980s. ASSIST will evaluate the effectiveness of proven tobacco control interventions implemented by 17 state health departments and their volunteer partners. The American Cancer Society (ACS) is a major contributor to this effort at the national, state and local levels. Tobacco control coalitions have been established and assessments of tobacco control activities and needs within each funded state were conducted. Based on this analysis, 5-year intervention plans were developed and implemented, employing proven tobacco control interventions, with a strong emphasis on policy interventions. Scientific evidence is strong that policy interventions achieve tobacco use reductions most effectively and efficiently. The emphasis on these interventions clearly distinguishes ASSIST from many earlier community tobacco control programs, including COMMIT.

Although legislation and other policies can decrease tobacco use, many questions remain regarding the effective strategies to develop, implement, enforce, and disseminate tobacco control policies. The NCI has funded a new initiative "Research in Innovative Strategies to Reduce Tobacco Use," with the goal to stimulate innovative behavioral, public health, and economic research on tobacco control policy interventions, and evaluate their feasibility, effectiveness and consequences. The results of this research should prove useful to policy makers and public health professionals responsible for enacting and enforcing effective tobacco control policies.

Smokeless (spit) tobacco continues to be the only tobacco product with increasing usage the U.S., especially among young males. The use of spit tobacco is no longer solely a rural phenomenon; its popularity is growing in urban areas and among white collar professionals. Few data are available on the specifics of cessation interventions related to these products and additional support to develop and evaluate pharmacologic and behavioral interventions is necessary. NCI has expanded its effort in the area of oral

cancer prevention through smokeless tobacco public education, cessation intervention, and primary prevention. In addition, NCI supports of the National Spit Tobacco Education Program (NSTEP) being coordinated with Oral Health 2000, the National Institute for Dental Research, and Centers for Disease Prevention and Control-Office of the Secretary for Health (CDC-OSH).

Cancer Surveillance

The NCI's Surveillance Program monitors the cancer burden on the U.S. population through the measurement of cancer incidence, mortality, and survival and the assessment of individual, societal, and health service factors that mediate these cancer measures. A major component of the Program is the Surveillance, Epidemiology, and End Results (SEER) Program, which consists of 11 population-based cancer registries covering 14 percent of nation's population. It is the major system for tracking cancer incidence, patient survival and mortality in the United States. One of NCI's highest priorities is to improve the nation's capability to measure cancer rates and risks for population segments such as minorities, the elderly, rural residents, and the underserved. With the recent expansion of the SEER Program, NCI now covers 25 percent of the Hispanic population, 41 percent of Asian/Pacific Islanders, 17 percent of the American Indian population (mainly in the Southwest) and 12 percent of the African American population. Collaboration with the Bureau of the Census is improving the availability of regional population data to calculate cancer rates for minorities, particularly those residing in SEER areas.

To foster additional collaborative research between academics in the fields of health economics and health services research and clinical researchers in cancer, a grant program announcement (PA) was issued in FY 1994 to solicit research proposals in three broad areas: cost of cancer treatment and care in various organizational settings; cost-effectiveness of cancer prevention and screening trials and interventions; and collection of economic data in the context of clinical trials.

Data from the National Center for Health Statistics and SEER program indicate that breast cancer mortality rates for American women declined 4.7 percent between 1989 and 1992, the largest such short-term decline in the United States for this disease since 1950. The decline for white women was 5.5 percent; however, African-American women did not experience a similar decline. Their breast cancer mortality rate increased by 2.6 percent over the same period. Research to understand the reasons for the declining rates in white women and the increasing rates in African American women is underway; influencing factors are thought to include differences in the use of adjuvant therapy, breast cancer awareness and screening with mammography and clinical breast examination, and changes in risk factors.

B. Cancer Treatment

Clinical Development of Paclitaxel (Taxol®) and Other Tubulin-Directed Agents

Paclitaxel is the first of a new class of anticancer drugs that has focused attention on tubulin and microtubules as critical targets for chemotherapy. These compounds bind to and stabilize microtubules and are thought to cause cell death by adversely affecting microtubule function during interphase and mitosis. Initial phase I/II studies have shown significant activity in refractory ovarian cancer (with response rates ranging from 20-50 percent), in metastatic breast cancer (with response rates of 20-62 percent), and promising activity in lung, head and neck, and esophageal cancers. Recent studies have focused on defining optimal paclitaxel dosing schedules and the role of paclitaxel in combination regimens. The Gynecologic Oncology Group has now reported survival data from a phase III study comparing paclitaxel plus cisplatin to standard therapy using cyclophosphamide and cisplatin in women with suboptimally debulked advanced ovarian cancer. The paclitaxel regimen was associated with a significant improvement in clinical response rate, an increased rate of negative second-look laparotomy, and improved median survival and acceptable toxicity. Other clinical trials investigating the combination of paclitaxel and other cytotoxic drugs in the treatment of breast cancer are underway.

The broad clinical activity and prolonged survival of women with ovarian cancer achieved with paclitaxel have stimulated renewed interest in other natural products and in tubulin binders. Phase I trials of dolastatin-10, the first tubulin binder from a sea organism (the marine mollusk, *Dolabella uricularia)* are planned. Continuing Phase II evaluation of CI-980 has revealed several interesting preclinical characteristics, including its resistance profile and activity in intracranial tumor implants in animal models. Other tubulin binders are being identified through the NCI screen and COMPARE evaluation, and criteria to prioritize their development are being considered. Agents with novel structures, varying mechanisms of action, activity in paclitaxel-resistant tumor models, or from previously unevaluated natural sources are of greatest interest.

Clinical Trials of Early Therapy versus Watchful Waiting for Low-Stage Prostate Cancer

The NCI/Veterans Administration (VA) "PIVOT" (Prostate Cancer Intervention vs. Observation Trial) for low-stage presentations in patients with at least ten years of life expectancy is viewed by CTEP as critical because it directly addresses the controversy regarding the six-fold increase in radical prostatectomies, the value of which is uncertain, especially in older age groups. Moreover, in the absence of data documenting the benefit of surgery (or radiation therapy), the assessment of screening strategies has been difficult or impossible. This phase III trial will compare prostatectomy with careful surveillance followed by treatment at clinical progression, with all-cause overall survival as the primary endpoint. In three years, PIVOT will accrue 2000 patients with T1-T2 tumors (with 12 more years of follow-up anticipated); about one-third of the patients will be recruited from Cooperative Group resources. Sophisticated videotape materials will be used to promote patient acceptance of randomization. Survival data will also be collected on the anticipated large numbers who refuse randomization so that an

assessment can be made of how representative the randomized group is of the potential prostatectomy population. In addition, survival results can be compared not only between the two randomized arms but also in relation to self-selected prostatectomy or radiation. This multi-group trial was launched in the Fall of 1994 and was recently designated an NCI high-priority trial.

The role of radiation therapy (RT) for clinically localized disease is no more firmly grounded in reliable data than the role of prostatectomy. However, since many of the VA hospitals do not have their own radiation facilities, and since a three-way randomization was felt to be too difficult, the PIVOT trial does not address radiation. For this reason, the North Central Clinical Trials Group (NCCTG) is leading the development of a parallel phase III Intergroup Radiation vs. Observation Trial for early prostate cancer, with a general design similar to PIVOT, randomizing between RT and watchful waiting.

Stem Cell Transfections

One potentially important application of retrovirally-mediated gene transfer into hematopoietic cells would be the expression of drug resistance genes to protect repopulated bone marrow from the toxicity of cancer chemotherapeutic agents. This strategy has been developed in mice, transfecting a multidrug resistance (MDR) gene into bone marrow cells using retroviral-mediated gene transfer and then returning the transfected cells to lethally irradiated mice. The MDR-transfected stem cells are able to reconstitute the marrow and, additionally, confer resistance to the effects of marrow-toxic chemotherapy agents that are eliminated by the MDR-encoded pump. Efforts are currently underway to test this method in humans. The first patients with advanced breast cancer have been treated with MDR-transfected bone marrow cells. It is hoped that the bone marrow will be repopulated with the resistant cells and that subsequent chemotherapy with drugs eliminated by the MDR pump will be tolerated with less marrow toxicity. If this approach is successful, this strategy could have broad applicability for enriching the bone marrow for a second non-selectable gene, such as ADA, by placing the MDR gene and the non-selectable gene on the same retroviral vector.

New Advances in Genetics - Colorectal Cancer

Study of families who are predisposed to colorectal cancer has shed much light on the genetic mechanisms which lead to colon cancer, not only in these individuals but also in sporadic (nonfamilial) cases. Two manifestations of hereditary colon cancer have been identified in the large majority of these families. Patients with familial adenomatous polyposis (FAP) develop hundreds to thousands of polyps in the colon and rectum usually by the time they reach their mid-twenties. Surgical resection of the colon is recommended for these individuals who face a near certainty of developing colon cancer by their early forties if left untreated. FAP, which probably accounts for less than ten percent of all U.S. colorectal cancer cases, has recently been associated with a germline mutation in the APC gene on chromosome 5q. Mutations found at this site in families with FAP typically result in an abnormally shortened APC protein. This finding has led

to a new approach to the molecular diagnosis of individuals with FAP which detects the presence of a shortened APC protein without the laborious process of identifying a specific mutation within a family with FAP. Studies are needed to validate this assay for use in identifying affected FAP family members. Normal APC protein appears to modulate interactions between the internal and external cell environment, ultimately affecting interactions between cells that are important in cell growth and development. This intriguing finding may suggest new targets for drug therapy. Mutations at this site are not limited to individuals with FAP but are commonly found in small adenomatous polyps and non-hereditary forms of colon cancer suggesting the fundamental importance of the APC gene in colon cancer development. NCI-supported investigators are assessing the prognostic significance of these genetic alterations in colon cancer.

A second form of hereditary colon cancer is referred to as hereditary non-polyposis colorectal cancer (HNPCC or Lynch's syndrome). Patients with HNPCC are defined by a family history with at least three affected individuals in at least two generations; one affected member must be a first-degree relative of the other two, and at least one must have developed the malignancy before the age of 50 years. HNPCC is estimated to account for three to six percent of new colorectal cancer cases annually. Unlike patients with FAP, patients with HNPCC do not develop polyps (although the presence of less than ten preexisting polyps at the time of diagnosis does not exclude an HNPCC diagnosis). A subgroup of individuals with HNPCC (Lynch syndrome II) also have an increased risk of other cancers, particularly endometrial, ovarian, urinary tract, and gastric malignancies. Studies of families with this syndrome did not show an association with the APC gene. Rather, in some families HNPCC was shown to be linked to a region on chromosome 2. Tumors from these families were found to contain DNA mutations that were most notable in regions containing simple repeated sequences (microsatellites). Tumors showed a marked variation in the size of these microsatellite regions (microsatellite instability); this pattern was felt to represent an inability to recognize and repair DNA mismatches that may occur during normal DNA replication. Tumors showing microsatellite instability are also referred to as replication error positive (RER+). An estimated 10-20 percent of sporadic colorectal cancers have been shown to be RER+. Unlike HNPCC, the sporadic RER+ tumors tend to occur in an older population and are not associated with more than one colonic tumor or tumors of other organs. These findings suggest that sporadic RER+ tumors may result from two somatic mutations within a colonic epithelial cell rather than a new germline mutation. Thus far, four genes have been linked to HNPCC; while these genes can be involved in sporadic RER+ tumors, over 50% of these malignancies appear to result from mutation(s) of other, as yet unidentified loci.

Anecdotal and some experimental data suggest that patients whose tumors manifest microsatellite instability have better long term survival than patients whose tumors do not have this property. Interestingly, rather than show an increased sensitivity to certain classes of conventional chemotherapeutic agents, cells that have a defect in mismatch recognition and repair are more resistant to alkylators. It is likely that this relative resistance is based on a complex interplay of DNA damage, repair, and programmed cell death (apoptosis). RER+ cells may not recognize the level of DNA damage that would induce apoptosis in a mismatch-competent cell. In addition, while more resistant to the

cytotoxic effects of alkylating agents, RER+ cells are more sensitive to the mutagenic effects of these agents.

NCI scientists, in collaboration with scientists from Johns Hopkins University, have determined the RER status of the eight colorectal and four ovarian cell lines used in the NCI drug screening program. This information has been used to analyze the results of studies on over 40,000 compounds to determine if there are classes of drugs to which RER+ cells are sensitive and to identify potential new agents that show a marked difference in activity based on RER status. This analysis confirmed RER+ cell line resistance to alkylating agents and showed them to be more sensitive to anti-metabolites than RER- cells. Perhaps more significantly, about 150 compounds showed differential activity in RER+ cell lines. These compounds provide new possibilities for treating individuals with RER+ tumors.

NCI and NCI-supported scientists are also developing strategies to study the efficacy of chemopreventive agents in selected patients at high risk for developing colon cancer. Agents showing chemopreventive activity in animal models include the nonsteroidal anti-inflammatory agents sulindac, piroxicam, aspirin, and ibuprofen as well as calcium, curcumin, and 18β-glycyrrhetinic acid. Preliminary clinical studies support the potential activity of sulindac and aspirin. Sulindac has shown dramatic effects in causing regression of colorectal adenomatous polyps in patients with FAP and Gardner's syndrome.

As part of a prospective study to define the prognostic significance of microsatellite instability, NCI scientists are collaborating with genetic counselors from the National Center for Human Genome Research (NCHGR). A determination of inherited disease risk has complex ramifications in terms of a person's self-image, family dynamics, psychological well-being, and insurability. In this and other studies, NCI-supported investigators are establishing a model structure for genetic screening activities that are certain to proliferate in both public and private institutions in the coming decades.

Cell-Free Molecular Screen of New Anticancer Drugs

Until recently, many pharmaceutical companies have used animal models and in vitro culture systems to screen potential anticancer agents. With a better understanding of cell growth control, particularly the molecular and biochemical pathways involved in growth factor signal transduction, new approaches to drug discovery are emerging. Protein tyrosine kinases (enzymes that phosphorylate and thus activate certain proteins) are involved in the early intracellular events in the pathways of many signals; serine/threonine kinases are involved in some pathways; and it is increasingly clear that phosphatases (enzymes that dephosphorylate some proteins) also play important roles in these pathways. Aberrant activity or loss of normal control mechanisms of one or more of these enzyme systems may be critical to the uncontrolled cell growth that is characteristic of malignant cells. In many cases, a single protein is capable of transforming cells. Inhibitors of critical enzymes could disrupt the signals, resulting in growth arrest. Several approaches will be used to identify new inhibitors of protein kinases or other components of the signal transduction cascade. It should now be

possible to develop a cell-free molecular screen for specific agents that modulate various enzymatic activities, such as the various protein tyrosine kinases, ras and other G-proteins, other components of cell signaling pathways, transcription factors, and structural proteins. NCI is initiating a concerted effort to develop these assays. In a related effort, each cell line in the 60-cell line Cancer Drug Screen is being characterized for the expression of various oncogenes, tumor suppressor genes, and drug resistance genes. These data will greatly increase the information content of screening results and may allow selection of natural products with specific inhibitory activity with as much confidence as will the molecular screen. Finally, new inhibitors will be rationally designed based on the active site of critical signaling enzymes or on common structural and electrochemical features of known inhibitors.

Clinical Development of Three New Melanoma Genes as Vaccine Candidates

Cancer vaccine development requires the identification of genes that encode tumor antigens that can be recognized by the cellular immune system (T cell mediated immunity). Coupling these genes (or their protein products) to immunization vectors may then be used to immunize patients against cancer antigens recognized by T cells. Researchers have recently identified, cloned, and sequenced three genes encoding melanoma antigens that are recognized by a special type of T cells (tumor infiltrating lymphocytes, TIL) that destroy cancer cells. Identifying the antigens recognized by TIL may be particularly useful in developing vaccines to boost the body's immune response against tumors. Two antigens, MAGE1 and tyrosinase, have produced clinically significant antitumor responses, suggesting that these antigens are important mediators of the antitumor response. A third antigen, the "melanoma antigen recognized by T cells" (MART) is an especially attractive vaccine candidate because it is expressed in virtually all melanomas. A MART vaccine is in preclinical development and should enter clinical trials in late 1995 or early 1996. Development of these and other vaccines will be advanced through a cooperative endeavor between intramural scientists and industry. NCI has entered into a Collaborative Research Agreement (CRADA) with Therion Biologics Corporation, which will generate vaccines using tumor antigens characterized by NCI scientists.

Genetic Engineering of Tumor Cells and Immune Cells Using Biologic Response Modifier Genes

In many common cancers (e.g. breast, colon), the immune system does not seem to recognize the cancer; as a result targeted immunotherapy to these cancers has been difficult. Perhaps the most exciting and best current application of gene therapy is the ability to introduce into peripheral blood lymphocytes (PBL) a novel T-cell receptor that recognizes tumor surface antigens identified by monoclonal antibodies (MOAb). Variable regions of MOAb are linked to the zeta chain of the T-cell receptor. When expressed in PBL, this novel receptor triggers the T-cell upon binding to the antigen target. This approach permits a huge array of antigens to be targeted on tumor cells previously recognized only by MOAb and the infusion of large numbers of 'clonal' functional T cells all recognizing the same tumor-related target(s). NCI scientists have shown that transduced T-cells can recognize and destroy ovarian cancer cells in vitro,

and can successfully treat mice bearing tumor cells expressing the ovarian cancer antigens. The first clinical trial will be conducted by NCI scientists using a receptor against a folate-binding protein (ovarian cancer). Similar receptor genes directed against colon cancer antigens have been designed and constructed. In addition to other common cancers, such as breast and prostate cancers, this approach may be applicable to adoptive immunotherapy for infectious diseases such as HIV and hepatitis B.

C. Cancer Etiology

Advances in Molecular Epidemiology

The ability to rapidly identify individuals who may be at increased cancer risk and the development of strategies to reduce or eliminate that risk is one of the most exciting new areas of research to emerge from the field of molecular epidemiology. NCI provides broad support for a wide range of molecular epidemiologic studies to increase understanding of environmental contributions, including occupational exposures, to carcinogenesis. Laboratory investigations of endogenous and/or exogenous factors are now an integral part of NCI epidemiologic study design. These factors include (1) inherited or acquired host factors that can elevate individuals' susceptibility to environmental carcinogens; (2) biomarkers that measure exposure to a potentially carcinogenic agent; (3) agents in the general environment that may pose carcinogenic hazards; and (4) specific environmental/occupational exposures that may be risk factors for special populations. NCI collaborates in many of these efforts with other agencies such as the National Institute of Environmental Health Sciences (NIEHS), Environmental Protection Agency (EPA), National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC) and other Federal agencies.

Identifying and characterizing intermediate endpoints, reliable markers of dietary intake, and molecular biomarkers using genetic and biochemical technologies will make it possible to monitor the effects of dietary changes on carcinogenesis and enable researchers to identify high-risk populations for intervention clinical trials. This promising new area of research is poised to answer the most fundamental questions in cancer etiology, prevention, and treatment.

Long Island Breast Cancer Study Project and Northeast/Mid-Atlantic Study

The Congressionally-mandated Long Island Breast Cancer Study Project, conducted under the joint auspices of NCI and NIEHS, seeks to determine the relative contributions of diverse environmental factors to elevated breast cancer risk in the New York counties of Nassau, Suffolk, and Schoharie and in Tolland County, Connecticut. This large epidemiologic study will examine a wide variety of environmental elements, including exposures to pesticides and other organochlorine toxins, drinking water contamination, indoor air pollution, aircraft and auto emissions, electromagnetic fields, hazardous waste, and municipal waste. Dietary factors, radiation, estrogen exposures, and occupational exposures are also being assessed. Also mandated by the Congress and jointly funded by NCI and NIEHS, the Northeast/Mid-Atlantic Study encompasses an

area covering the District of Columbia and nine states from Maryland to New England. The goal of this epidemiologic study is to define and quantitate the contributions of a number of environmental factors, particularly pesticide exposures, to breast cancer risk.

Helicobacter-Associated Cancers

A new bacterial species, *Helicobacter hepaticus*, was discovered in 1992 at NCI's Frederick Cancer Research and Development Center. *H. hepaticus* selectively and persistently colonizes the bile channels of mice. Infected animals develop a morphologically distinctive pattern of chronic active hepatitis, followed by hepatic lesions that quickly progress from adenomas to hepatocellular carcinoma. *Helicobacter*-associated chronic active hepatitis acting as a premalignant lesion represents an altogether new animal model to study mechanisms of carcinogenesis by *Helicobacter* species in which persistent bacterial infection leads to tumor development. The recently demonstrated association between *Helicobacter* infection, the development of mucosa-associated lymphoid tissue (MALT), and the occurrence of primary B-cell gastric MALT lymphoma in humans, as well as a report of neoplastic lesions in mice infected with a strain of *Helicobacter*, suggest a wider role of these organisms in cancer etiology.

D. Tumor Biology and Immunology

Cyclin D1 and Breast Cancer

Cyclin D1 is a cell-cycle regulated protein required for transition of cells from G1 to S phase that appears to be overexpressed in some human cancers, including breast cancer. Recent studies suggest that cyclin D1 can act as an oncogene. Cyclin D1 over-expressing transgenic mice develop mammary hyperplasia that eventually develops into adenocarcinoma and stable overexpression of cyclin D1 in rodent fibroblasts enhances their tumorigenicity in nude mice. In addition, the breast tissue of mice lacking cyclin D1 fail to undergo the normal epithelial cell proliferation associated with pregnancy, suggesting that cyclin D1 plays an important role in steroid-induced proliferation of mammary epithelium.

Loss of T-Cell Immunity in Cancer Patients

There are many immune-based cancer therapy strategies that work well under experimental conditions, but have failed to show benefit in the clinic. Recent discoveries have shown that this may be due to the fact that animals and humans who have had cancer for any appreciable period of time have a critical component of the immune system shut off. T cells, which regulate the cellular arm of the immune system, are unable to respond to normal stimuli in tumor-bearing individuals. In some cases, the nonresponsive T cells are limited to the area within and around the growing tumor; but in other cases, all or most of the T cells in the blood are similarly affected. The discovery and characterization of this immune defect explains many of the failures of active immunotherapy. Development of methods to prevent or reverse T-cell inactivation in cancer patients may lead to substantial improvements in the clinical usefulness of cancer vaccine strategies and other approaches to immunotherapy.

Mutations in the TGF-β Receptor

Cell proliferation is regulated by a balance of inducing and suppressing factors. One potent growth inhibitor is tumor growth factor-beta (TGF-β). Because tumor cells are frequently refractory to growth suppression by TGF-β, the mechanism responsible for loss of this response might help to explain the growth of tumor cells. It was recently found that the cellular receptor for TGF-β is mutated in a large number of tumor cell lines, indicating that transmission of the ligand's signal may be blocked. TGF-β receptor gene mutations in colon carcinoma cell lines appear to result from an inability of the cells to repair DNA damage; this presents one pathway through which a cancer cell can subvert normal growth suppressing signals.

Gene Inactivation by Methylation

The expression of genes can be altered by methylation of the DNA, a prevalent, sometimes crucial, event in some malignancies. In many non-familial kidney cancers, the Von Hippel-Lindau (VHL) tumor suppressor gene is methylated; the gene is not transcribed and normal VHL protein activity is lost. Recently the loss of estrogen receptor (ER) activity as a result of methylation has also been reported. ER-negative human breast tumors have a poor prognosis. New data also suggest that ER gene inactivation by methylation in aging colon mucosa is an early event in development of non-familial colorectal tumors. Restoration of normal gene activity may be possible with demethylation agents, a new type of gene-targeted therapy.

Interleukin-12 in Cancer

Cytokines are substances that enable different cells of the body to communicate with one another. Interleukin-12 (IL-12) is a cytokine largely confined to cells of the immune system that has shown a wide range of beneficial effects in cancer therapy in experimental animals. Clinical studies are at an early stage, but already IL-12 has demonstrated an ability to correct the immune abnormalities found in Sezary Syndrome (an advanced form of cutaneous T-cell lymphoma), and to improve immune function in AIDS patients by improving the ability of T cells to kill pathogenic bacteria and other organisms. While IL-12 appears to have some toxicity in humans, its ability to stimulate the killing of many tumor cells, along with its ability to stimulate effective immune responses, make it a very promising therapeutic agent.

Development of a HPV Vaccine for Cervical Cancer

Certain types of human papillomaviruses (HPVs), especially HPV16, are strongly associated with malignant progression of genital lesions. Two HPV genes, L1 and L2, encode the proteins that form the viral coat of the virus, and thus represent promising candidates for an HPV vaccine. Virus-like particles (VLPs) for HPV16 and other HPVs that consist of L1 or L1 plus L2, have been generated to explore the potential utility of VLPs as a prophylactic vaccine. Trials have been conducted in two animal models, rabbit and cow. In each case, the VLPs induced high titers of neutralizing antibody and

provided protection from infection for the HPVs tested. The absence of HPV16 infection in young children and teenage girls prior to initiation of sexual activity supports the conclusion that a prophylactic vaccine could be effective if administered prior to that event. Recent studies have demonstrated that virions from two geographically distinct and genetically divergent HPV16 variants are serologically cross-reactive. This suggests that vaccination with the VLPs of a single HPV16 variant might afford worldwide protection from infection and subsequent risk of cervical and other anogenital cancers.

III. CONCLUSIONS

In 1994, an estimated 1,208,000 Americans were diagnosed with cancer, and approximately 538,000 people died of cancer. Significant mortality reductions for some cancers and improved technologies across the continuum of cancer care have been achieved, yet overall survival has improved only modestly since 1973 while incidence and mortality continue to rise.

Despite these solemn statistics, the National Cancer Program (NCP) has, over the past 25 years, made tremendous inroads into understanding the extraordinary complexities of the more than 100 diseases we call cancer. The public and private efforts that have given the American people this knowledge should not be diminished. Without question, the fruits of American investment in cancer research and cancer care delivery are shared in hospitals and laboratories around the world. The perpetuation and extension of these successes must be one of the central goals in Federal research support, but the NCP must be effected in a more coordinated manner to speed the application of research findings in the community. Because the National Cancer Program encompasses not only cancer research, but all public, private, voluntary, and individual activities that impact our national cancer problem, all of its participants must join forces to most rapidly reduce the national suffering and burden due to cancer. If we are to achieve these critical goals, however, 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 diversity.

We know that many cancers are avoidable, and responsible public policy and targeted public education can do much to safeguard and empower the people to protect their own health. Fifty percent or more of cancer incidence is attributable to individual behaviors that include smoking and inadequate or inappropriate diet. Our inability, as a Nation, to alleviate these preventable causes of cancer must be remedied. As stated in our previous transmittals, a strong national stand against tobacco use by teenagers must be maintained, regulations on the same should be promulgated by the Department of Health and Human Services, and the decision by the FTC to review and revise its stipulations on cigarette labeling should be rigorously supported.

In light of the testimony heard by the Panel since its last report to you, it is our overarching recommendation that the National Cancer Program address immediately one issue that spans the breadth of cancer research and its conversion into routine medical

and preventive cancer care practices--the use and misuse of the knowledge we have already amassed during the first quarter century of the Program.

This recommendation encompasses enhanced health education for our future generations; improved communication within the scientific community and between that community and its investors, the American public; and clarification of the implications of new technologies that have allowed us to achieve such feats as creating genetic pedigrees and applying that information to the prediction of lifetime cancer risk.

Specifically, the goals of the National Cancer Program should include:

1. Improved data collection and data sharing.

2. Development and implementation of a national curriculum, beginning in the primary grades and continuing throughout the school years, that fosters health promoting behaviors and nurtures personal responsibility for maintaining a healthy lifestyle. Emerging needs for health professional and research training must also be addressed.

3. Enhanced public and private support for and participation in clinical research.

4. Careful consideration of ethical, legal, social, economic, and privacy concerns associated with emerging genetic and related technologies and their impact on the individual.

DATA COLLECTION AND SHARING

Information technology is advancing at a breakneck, yet still accelerating pace. Many of these technologies will facilitate the ability of all Americans to rapidly access information, including health and scientific information. This same technology, however, is creating a new potential to isolate underprivileged Americans who may not have access to phones and rural or inner city physicians who may lack both the funds and the time to surf the Internet. Greater freedom of access also increases the likelihood that information will be available that has not be subjected to a strong scientific quality control process. The Panel recommends that:

- The data systems that form the information infrastructure of the National Cancer Program be re-examined--they are uncoordinated, not uniformly accessible, and largely without guidelines that address ownership or confidentiality of much of the data therein. Data collection forms the fundamental support of our entire research effort and must be strengthened through standardization, quality control, and the ethical protection and appropriate sharing of data.

- As the data infrastructure also forms the basis for research evaluation, insurance evaluation of patient populations, and assessments of the impact of new treatment and prevention modalities, better algorithms are required to distinguish among our populations and evaluate their needs. Many of our baseline assumptions in

basic, clinical and population-based research must be reassessed in the context of their intended research applications.

- The trend in information technology toward delivery-on-demand will bring much more information directly into the hands of the American public--in effect, it will greatly shift the balance of power between researcher and consumer, and between doctor and patient. Physicians and researchers must be prepared for and embrace this new relationship.

- The research community must take a more active role in endorsing and expanding current efforts require truth in advertising as it relates to individual health; examples include issues related to individual smoking behavior and tar and nicotine levels in cigarettes, claims regarding the fat content of foods, and needs for vitamin or mineral supplements. All such claims must be backed by sound science and readily understandable to all segments of the public.

EDUCATION

Individuals' behavioral practices develop from lessons begun early in life. To decrease cancer incidence and mortality in the future, it is crucial to incorporate research results in early education aimed as establishing personal responsibility for individual health maintenance. Reinforcement of health promoting behaviors should be maintained throughout life. This should be achieved by:

- Strengthening education related to health promoting behaviors beginning in the primary grades.

- Developing criteria for ongoing evaluation of the success with which health education lessons are implemented.

- Providing opportunities (e.g., school-based and community athletics programs) and incentives (e.g., health insurance premium reductions) that reinforce the importance of personal health behaviors.

- Supporting health promoting education of young people through continued and more rigorous enforcement of national and local penalties for sales of tobacco and other regulated, potentially cancer-causing agents to minors.

Education is also needed to ensure that current and future generations of researchers and clinicians are able to make maximum use of exploding information resources and technologies. Specifically, we must:

- Restructure graduate level curricula of all types to meet to future research data needs; for example, training is needed to develop patient history and other data collection skills adequate to support evolving basic, clinical and population based research data requirements.

- Recognize that informatics has become a primary research tool--any research training must provide the necessary skills for navigating existing and future information resources for basic, clinical, and or population-based research.

ENHANCED SUPPORT OF CLINICAL RESEARCH

Clinical research, particularly translational research, is increasingly endangered by fiscal constraints posed by health care payment mechanisms that eliminate patient care revenues that previously augmented government research support, and by related economic forces. Wider and more consistent dissemination of research results must be made to assure that the public and private sectors both understand the need for and the value of research to identify and address clinical problems in cancer. It must be made clear that cancer research is conducted for the benefit of all populations, and that clinical research makes an irreplaceable contribution to reducing the cancer burden and the staggering health care costs and productivity losses associated with cancer. To achieve these goals, the Panel recommends:

- Establishing profiles of key users of research results (e.g., health care payers, community physicians, other health professional groups, legislators) and developing targeted, population-specific strategies to communicate successes in and the value of clinical research.

- Examining the existing relationship between managed care and clinical research and establishing mechanisms to encourage participation by managed care systems in clinical research and ensure access to clinical trials for managed care subscribers.

- Cultivating a mechanism for and developing active support for outcomes research to evaluate the costs and benefits of clinical trials and the applications of that knowledge to all Americans.

- Expanding participation in the national cancer effort, including clinical research, through an active strategy to identify and engage the core strengths of a wide range of public and private sector constituencies. Sharing information, resources, and capabilities in a framework founded on collaboration will strengthen the National Cancer Program as a whole and enable the implementation of efforts to reduce the cancer burden that extend beyond the scope of Federal authority alone.

- Providing appropriate incentives to pursue careers in clinical research, including training, jobs, career opportunities, and grants availability.

ISSUES RELATED TO EMERGING TECHNOLOGIES

Our knowledge of the genetic basis of cancer and the molecular mechanisms that lead to the transformation of normal cells to cancer cells is advancing faster than our ability to

properly address the ethical, psychosocial, medical, legal, and economic ramifications of applying this knowledge in the community.

- Knowledge concerning human genes and their role in cancer must be disseminated in a controlled manner that does not create the potential for employment or insurance discrimination based on genetic heritage.

- Genetic testing should be limited to the research arena until the economic and psychosocial impact of test results are assessed and appropriate supportive mechanisms (e.g., genetic counseling) and protective legislative measures are in place.

- Personal genetic information must be closely guarded; furthering the research mission of the National Cancer Program must not jeopardize individual consent and privacy.

- Similar strategies should be considered for all scientific breakthroughs of similar import for the American public.

NATIONAL CANCER INSTITUTE

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