January 1 to December 31, 1991

President's Cancer Panel

Report of the Chairman

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

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PRESIDENT'S CANCER PANEL

National Cancer Program • National Cancer Institute

Acting Executive Secretary
Iris J. Schneider
Assistant Director
National Cancer Institute
Building 31, Room 4A34
Bethesda, MD 20892
PHONE: 301-496-1148
FAX: 301-402-1508

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

Dear Mr. President:

The Health Omnibus Extension Act of 1988 requires the Chairman of the President's Cancer Panel to submit a report to you each year on the status of the National Cancer Program. Accordingly, I am pleased to submit my report for 1991 as enclosed.

I and two other members of the Panel, Mrs. Nancy G. Brinker and Dr. Geza J. Jako were all appointed in 1991, following the death of the previous Chairman, Dr. Armand Hammer, and the resignation of his colleagues.

As you know, in December of 1991 we celebrated the 20th anniversary of the signing of the National Cancer Act and the declaration of the war against cancer by President Richard M. Nixon. At that time, he established the President's Cancer Panel, which I now have the privilege and responsibility of chairing. Americans can be proud of the progress that has been made in large part due to the research stimulated by the National Cancer Act. Dramatically increased cure rates in childhood cancers, Hodgkin's disease, and the leukemias along with significant breakthroughs in achieving an understanding of the fundamental molecular changes which explain carcinogenesis are some of the measures of this progress.

But even as we celebrate progress, it is sobering to note that within this year one million Americans will develop cancer and one half million will die. It is also important, Mr. President, to note that some Americans have not substantially benefitted from the great advances that have been made. To illustrate this point, note that poor Americans, irrespective of race, have a 10 to 15 percent lower five year survival rate compared to other Americans. This low survival is primarily related to late diagnosis and advanced disease at time of diagnosis. Currently, there are 35 million poor Americans overlapping 35 million uninsured. One of four Americans is poor, uninsured, or both.

Since becoming Chairman of the President's Cancer Panel, I have expanded the scope of issues addressed by the Panel to a broader consideration of the National Cancer Program, which is not limited solely to issues which can be addressed by the National Cancer Institute. This expansion of scope, I believe, is consistent with the original intentions of President Richard M. Nixon when he initiated the National Cancer Act in 1971. President Nixon indicated at that time that he would direct the full power of the President, the Cabinet, and the Legislative Branch of government in conducting the war against cancer. This expansion in the scope of the Panel's activity is also in keeping with the reality that cancer always occurs in individuals who live in specific human circumstances. Such social and economic circumstances are often the critical determinants of whether one will survive or die.

With these thoughts in mind, in my first year as Chairman, the Panel has explored the relationships between poverty and cancer. Research has shown that conditions associated with poverty such as diminished access to health care, risk-promoting life style, and substandard living conditions are factors which lead to late diagnosis and high death rate in this population of Americans.

The President's Cancer Panel concludes that these human factors create a major barrier to the full implementation of the goals of the National Cancer Program. While on one hand, under the superb leadership of Dr. Samuel Broder, the National Cancer Institute is carrying out its charge by advancing the country significantly forward in cancer research, we have failed to sufficiently apply these advances to all segments of the American population.

In 1983, the National Cancer Institute took on a new approach to the war against cancer when it set a goal to diminish the mortality rate from cancer by 50 percent by the year 2000. The achievement of such a goal requires that we sustain our research progress against this disease, and accomplish a dramatic narrowing of the gap in cancer incidence and survival between the socioeconomically disadvantaged and other Americans. To reach this year 2000 goal, we must tear down the economic and cultural barriers to prevention, early detection and treatment of cancer by extending the war against this disease to the neighborhoods of America where people live and die.

The designated battlegrounds for waging such a "guerrilla war" therefore should include geographically and culturally delineated areas of high cancer incidence and mortality. Such areas should be targeted with intense approach to providing culturally relevant education, control of tobacco use, and appropriate access to early diagnosis and treatment.

The National Cancer Institute is not empowered to conduct this war alone. A successful ground war against cancer requires that the Congress and the Executive Branch of government have the unwavering political will to win this war and that the American people become foot soldiers in this fight for their own lives.

Therefore, I make the following recommendations:

- Continue and augment funding of basic research through the National Cancer Institute.
- Provision of access to cancer prevention, diagnosis, and treatment to all Americans.
- Delineation of geographical and cultural areas of extreme excess of cancer mortality in America. Such areas should be designated as CHRONIC DISASTER AREAS and be provided with special Federal and local assistance with respect to education and access to health care.

My appointment as Chairman of the President's Cancer Panel is a great honor and a great responsibility. I and my colleagues are truly privileged to have a major role in monitoring and guiding the National Cancer Program. The challenge and the task are difficult but there is great promise through this Program for greatly reducing death and suffering from cancer in this country and throughout the world.

I hope this report and these recommendations will be useful to you and the members of your Administration in planning for the future.

Sincerely,

Harold P. Freeman

Harold P. Freeman, M.D.
Chairman

Enclosure

REPORT OF THE CHAIRMAN - 1991

The 20th anniversary of the National Cancer Act was celebrated in 1991. Twenty years ago the Congress of the United States made a commitment to the American people to reduce the suffering and dying due to cancer. To achieve this goal the Congress created the National Cancer Program. The wisdom of this cohesive and comprehensive approach to cancer research and control is quite apparent.

When the National Cancer Act was passed, surgery was the primary treatment for cancer; radiotherapy was being developed and chemotherapy was in its infancy. Strategies were just being developed to allow for more intensive therapy, such as the use of empiric combinations of antibiotics and the availability of supportive platelet transfusions. The concept of "curability" was so bold as to be almost unthinkable. Since then, major progress has been made in reducing deaths from childhood cancers - a reduction of 38 percent since 1973, with almost two-thirds of children with cancer surviving to the five year "cure" landmark and beyond. The astonishing progress against Hodgkin's disease, for which there has been a 50 percent reduction in death rate, or against testicular cancer, for which there has been a 60 percent reduction, is well-recognized. But there has been progress against several of the more common adult malignancies, as well, mainly for individuals under the age of 65. For example, in this age group, the death rate for colon cancer has fallen by approximately 16 percent, for ovarian cancer by about 25 percent, for cervical cancer by about 40 percent, and for bladder cancer by more than 30 percent.

The NCI reviews the annual cancer statistics on morbidity and mortality and sets its priorities accordingly. This process has brought new programs and research focused on a number of groups in special need; minorities, the medically underserved, and women, while continuing its basic research programs for all forms of cancer.

Many of the recent therapeutic innovations offer patients an improved quality of life as well as a chance for longer life. With breast cancer, for instance, treatment has advanced toward earlier and more accurate diagnosis, less invasive surgery, breast reconstruction, and increased survival. For osteosarcomas, colorectal cancers, and bladder cancers, we are more adept at avoiding radical organ removal or functional impairment and preserving organs that define an individual's autonomy and independence. For cancer of the larynx, we can more frequently preserve function and save the ability to speak, a gift of immeasurable value. Despite rewarding progress and promise in these and other areas, we still have much unfinished business and many urgent challenges.

The President's Cancer Panel, presently consisting of myself as Chairman, Mrs. Nancy G. Brinker of Dallas, Texas, and Dr. Geza J. Jako of Boston, Massachusetts, began our terms in office in April, 1991. The first Panel meeting was held in Bethesda, Maryland, in July. The hearing focused on Cancer and Poverty. Testimony was presented providing evidence and statistics

to better understand the national problems and needs. Dr. Louis W. Sullivan, Secretary of the Department of Health and Human Services, Dr. Bernadine Healy, Director of the National Institutes of Health, Dr. Samuel Broder, Director of the National Cancer Institute, and other noted experts in the fields of sociology, anthropology, epidemiology, and clinical and basic oncology provided data and expertise to the Panel.

Much of the data presented and discussed at the Panel hearing support the conclusion that poverty causes cancer and cancer causes poverty. We as a nation must develop effective interventions for the prevention and cure of all forms of cancer. We must develop comprehensive and long-term solutions for those are at highest risks, both medically and economically.

Poverty knows no race, color, or religion. Poverty, lack of access to medical care, and lack of ability to pay for care when available, is a great leveler. In this country many of the poor are members of minority groups or groups that for one reason or another are medically underserved.

The President's Cancer Panel held its second meeting at the Morehouse School of Medicine in Atlanta, Georgia, in September, and was concerned with Training in Science. Presentations were made by experts in advanced and elementary education areas, from the corporate sector, and by program specialists who have observed educational progress in minority and disadvantaged communities in the nation.

There were clear indications presented that we are approaching a crisis in science and medical education. Who will be the scientists and clinicians of the future must be seriously considered. This issue has important implications for the alleviation of suffering and the reduction of deaths from disease. We as a nation must have a significant effective science infrastructure to compete successfully in the world in the 21st century.

The third Panel meeting was held December 9th, at the M. D. Anderson Hospital and Tumor Institute in Houston, Texas. The hearing focused on Breast Cancer Research. Breast cancer is the second leading cause of cancer death in women. Statistics reveal that the risk of developing breast cancer increases with age. While we have made some progress in the mortality rates for younger women, the statistics have not improved in other categories. For white women under the age of 50 with breast cancer, mortality has decreased by 13.5 percent since 1973. However, while mortality rates for leukemia and cancers of the breast, larynx, pancreas, colon, and rectum are steadily decreasing for whites, they are increasing for African-Americans.

In Houston, Dr. Charles LeMaistre, President of the University of Texas, M. D. Anderson Cancer Center and Dr. Frederick F. Becker, the Scientific Director of the Tumor Institute, provided excellent overviews of the world and national circumstances in relation to cancer research, with specific emphasis on breast cancer research. Twelve additional experts testified to the Panel regarding progress in clinical research, breast conservation measures, new therapies and discoveries in the biology and genetics of breast cancer, and proposed possible preventive measures.

Evidence was provided that some of the greatest advances in cancer are being derived from the techniques developed to insert a small piece of human DNA into a bacterium or a plasmid or a virus. The Panel was told that this technological achievement spawned a revolution in molecular genetics and our understanding of biology that bodes extremely well for cancer treatment, diagnosis, and perhaps prevention.

SUBPANEL ON BREAST CANCER

The Panel has launched a significant new initiative in breast cancer in women. Vice President Quayle requested the President's Cancer Panel to establish a special Subpanel "to undertake a detailed study of the state of breast cancer research, detection, and treatment in the United States and around the world."

In response to the Vice President's request, the Panel has established a sixteen membered Special Commission, chaired by Mrs. Brinker. This Subpanel's mission is to provide a carefully considered and comprehensive evaluation of the most promising approaches to reduce the suffering and death due to breast cancer. The Panel will present the report of this Special Commission to the White House in 1993 at the conclusion of its intensive study.

This report will outline and discuss the advances achieved by the National Cancer Program in 1991.

CANCER PREVENTION

The National Cancer Institute carries out a comprehensive program of basic and applied research in its Cancer Prevention and Control Program. It also conducts surveillance and monitoring of the incidence, mortality and morbidity of cancer. A priority for the Cancer Prevention and Control Program is to conduct prevention research and to develop strategies for health promotion activities for the nation.

In 1991, the NCI launched its largest smoking intervention program, the American Stop Smoking Intervention Study (ASSIST), in collaboration with the American Cancer Society (ACS). The program incorporates information from the NCI, state and local health departments, and disseminates the knowledge in collaboration with the ACS volunteer corps. Smoking is known to contribute to the development of lung cancer as well as other cancers. It continues to be responsible for a third of all cancer deaths. The ASSIST program will reach 90 million Americans, including about 70 million smokers. A major emphasis of ASSIST outreach efforts includes minority and underserved sectors of the population.

Research in the Cancer Prevention Research Program is divided into two broad categories: Diet and Nutrition, and Chemoprevention. These are pursued through both intramural and extramural mechanisms.

A number of intervention studies involving NCI researchers in the United States and abroad have been initiated in nutrition and prevention trials. These projects represent collaborative efforts investigating dietary and constitutional factors relating to cancer prevention. In China, nutrition intervention studies testing the efficacy of multiple vitamins and minerals in the prevention of esophageal cancer mortality are nearing conclusion in an NCI-sponsored study of 34,000 subjects. In Finland, beta-carotene and vitamin E are being tested as lung cancer chemopreventive agents in 29,000 smokers.

The Polyp Prevention Trial has been initiated and is one of the NCI's first large trials in which the intervention strategy involves dietary modification. In this trial, the diets of subjects will be modified to include low-fat, high-fiber, and enhanced vegetable and fruit consumption in an effort to prevent the recurrence of adenomatous polyps of the colon, which are known to be cancer precursors.

A major study focusing on breast and colon cancer is planned to evaluate the effect of dietary differences on cancer risk. The study will involve 200,000 to 400,000 elderly participants. Additional research initiatives regarding carotenoids, other than beta-carotene, will continue and be expanded in the search for specific nutritional components in fruits and vegetables that inhibit cancer.

The Prevention Research Program's new Laboratory of Nutritional and Molecular Regulation began operation at the NCI-Frederick Cancer Research and Development Center. This new laboratory will study the fundamental processes regulating growth and their relationships to cell mutations.

The Chemoprevention Program is sponsoring 41 human efficacy chemoprevention trials designed to determine the potential for chemoprevention, and the effective regimens for the reduction of cancer incidence. Study participants include individuals from the general population, individuals at high risk for cancer (because of occupation, life style, or place of residence), individuals with preneoplastic lesions, and patients with previously treated cancers.

Several trials using a synthetic derivative of vitamin A, 13-cis retinoic acid, to prevent cancer in high risk individuals have been concluded. In one trial patients with previous head and neck cancers who were treated with 13-cis retinoic acid had significantly lower rates of new malignancies than placebo-treated controls.

New trials have been initiated in the National Clinical Trials Network to test the anti-estrogen tamoxifen as a breast cancer chemopreventive in women who are at high risk. In women who have had one breast cancer, tamoxifen, in many clinical trials, reduced the incidence of cancer in the opposite breast by 40%. Scientists now estimate that tamoxifen has the potential to significantly reduce the incidence of breast cancer in high risk women.

Based on the report of the Secretary's Task Force on Black and Minority Health in 1983 and recent data on cancer incidence, morbidity and mortality, NCI has established major initiatives to address the needs of minorities, low-income groups, and other medically underserved populations. Populations include

Black Americans, Native Americans (American Indians, Alaskan Natives and Native Hawaiians), and Hispanic populations as well as low-income, inner-city and other medically underserved populations.

Outreach programs recently initiated by the NCI to bring screening and other health care modalities to underserved populations include the Washington, D.C. Mammography Education Initiative, and collaboration with the National Medical Association, to support the Mammography Education Project for African-American Women. The NCI Black Leadership Initiative incorporates community-based action efforts to address women's health.

The NCI, in cooperation with the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the American Cancer Society (ACS), and state health departments, has organized outreach strategies that will provide and maintain breast and cervical cancer screening nationwide. A Forum on Breast Cancer Screening in Older Women was held in January 1991 to discuss recommendations to improve utilization of physical examinations and mammography for women aged 65 and over. The Institute is supporting a new initiative that targets early detection, diagnosis, treatment decisions, and comprehensive medical management of breast cancer in these women. NCI continues to work with the Health Care Financing Administration on guidelines for reimbursement for breast and cervical cancer screening for Medicare beneficiaries.

CANCER TREATMENT

Since the passage of the National Cancer Act, cancer treatment has advanced in the areas of surgery, radiation, and chemotherapy. Now an additional modality has been added to standard cancer treatment: biological response modifiers. Research has led to an astonishing advance in the ability to isolate and intensify the natural elements of the human immune system to fight cancer and other diseases. In the last year, two elements important in bone marrow cell production, G-CSF and GM-CSF were approved by the Food and Drug Administration, now making them available for patients undergoing chemotherapy or radiation.

NCI's ability to quickly transfer new laboratory and experimental advances to clinical practice depends on national resources such as the Cancer Centers Program, the Clinical Cooperative Groups, and the Community Clinical Oncology Program (CCOP). A Minority-Based CCOP was initiated to provide minority cancer patients with access to state-of-the-art cancer treatment and control technology. Twelve programs have been funded for three years. They will include more than 50 percent of new cancer patients entering clinical trials coming from minority populations. These programs were initiated in Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, New York, two in Texas, and in Virginia, The District of Columbia, and Puerto Rico.

Rapid and effective technology transfer is essential to the success of the National Cancer Program. In 1991, NCI scientists and colleagues from the National Heart, Lung, and Blood Institute continued the development of gene therapies. Last year researchers treated a four-year old girl with an

extremely rare, inherited immune system disorder caused by the absence of the enzyme adenosine deaminase (ADA). As a result of the gene therapy, she has had considerable restoration of her immune function and has started school. Another patient, a nine-year old girl, has begun treatment, and a third patient will begin treatment in the near future. A new gene therapy trial for malignant melanoma also began in 1991.

Gene therapy is now being investigated by the NCI in cancer patients at the NIH Bethesda Clinical Center. FDA approval to initiate these studies was obtained in 1991. Dr. Steven Rosenberg, Chief of NCI's Surgery Branch, and his colleagues, have begun this work potentially initiating an era of extraordinary significance.

Adoptive immunotherapy is an evolving treatment approach in which a patient's own immune cells are removed from the body, modified to become more effective in attacking and destroying tumor cells, and then replaced. Immunizing a patient with a vaccine designed against the patient's own tumor, and the use of monoclonal antibodies designed to search out and destroy tumor cells are examples of active specific immunotherapy currently in clinical trials.

Clinical scientists at the NCI have shown that human tumor infiltrating lymphocytes (TIL) can recognize tumor-specific antigens on human melanomas. These new techniques have enabled scientists to identify tumor-specific antigens on other tumors such as breast cancer, renal cell cancer, and bladder cancer. The antigens are tumor-specific, and not present on normal cells. Patients who have had their tumor removed by surgery and who are at high-risk of having metastatic disease, are now also receiving tumor-antigen vaccines as part of their treatment.

Ongoing research is directed towards inserting specific genes into human TILs to increase their tumor killing capacity. Studies include inserting the gene for tumor necrosis factor into patients' TIL cells. There is great potential for this modality in the treatment of a wide variety of diseases.

Seven anti-cancer agents were approved by the FDA in 1990 and 1991. These are BCG for bladder cancer, levamisole as adjuvant therapy in colon cancer, fludarabine phosphate for refractory chronic lymphocytic leukemia, hexamethylmelamine for ovarian cancer, idarubicin for acute myelogenous leukemia, G-CSF and GM-CSF for neutropenia in chemotherapy and deoxycoformycin for hairy cell leukemia. Each of these has resulted from NCI-sponsored clinical trials over the past decade.

In its intensive efforts to identify effective new anti-cancer drugs, the screening of new synthetic and natural products continues at the NCI at an annual level of about 20,000 substances, utilizing a test panel of 54 human tumor cell lines in culture. Over 600 substances have been selected for further review and evaluation, based on tumor specificity, potency, and other characteristics.

One of the most promising new drugs, taxol, interferes with the process of cell division, thus, stopping the proliferation of cancer. Taxol has been found to cause regressions in many ovarian and breast cancers which were

refractory to other therapies. New programs for cancer treatment have resulted from the application of basic studies of the cell cycle and the newly discovered biochemical regulation of these cycles.

Many new treatments offer patients an improved quality of life as well as a better chance for cure. Breast cancer treatment has advanced toward better diagnosis, less invasive surgery, breast reconstruction, and often increased survival. It is now possible, in many cases of colorectal cancer and bladder cancer, to prevent colostomies and preserve organs that help define an individual's autonomy and independence. It is now possible to preserve the voice box and the ability to speak, thus retaining personal identity and communication skills in patients with cancer of the larynx.

The great significance of these gains in terms of the quality of life for cancer patients should not be underestimated.

CANCER ETIOLOGY AND MOLECULAR GENETICS

Early stages in cancer development, frequently called dysplasias, are typically associated with an abnormal amount of cell division. Mutations are extremely infrequent events in mammalian cells and become established only during cell replication. In many studies it has been observed that two or more cell mutations are necessary to initiate cancer development. Human malignancies which involve an inherited mutation are very rare, but they have provided a great deal of information about the molecular genetics of cancer. Children born of families that carry a defective gene, such as the retinoblastoma gene, inherit a "first genetic event." Subsequent genetic alterations of cells have been followed closely in these families, to detect their cancer promoting potential.

Although carcinomas differ in etiology and pathogenesis, some unifying themes have become apparent. In cells that convert to cancer, these themes are: oncogene expression is induced; tumor suppressor genes, which typically function to maintain normal growth, are inactivated or completely lost; and areas of certain chromosomes are lost or rearranged. Significant progress is being made in defining the actions of both these positive (oncogenes) and negative (suppressor genes) regulators of cancer expression.

One suppressor gene of great importance is p53. Mutations in the p53 gene are emerging as the most common form of genetic error in human cancers. The normal version of the p53 gene, present in most human tissues, suppresses abnormal cell growth. Mutated p53 loses its suppressing activity and becomes a tumor promoter.

The retinoblastoma tumor suppressor gene (RB) is defective only infrequently in ovarian tumors. The findings imply that inactivation of both suppressor genes, RB and p53, is important for the development of ovarian tumors. Other suppressor genes appear to be involved in the early initiation of ovarian cancers.

Research is underway to identify the suppressor genes now known to be on chromosomes 6 and 17, so that their functions can be resolved. These genes may be general suppressors for tumors of epithelial origin, or they may be specific for ovarian tumors.

Ovarian carcinoma accounts for about six percent of all cancer deaths in females, and 47 percent of deaths from female genital malignancies. There are about 20,000 new cases of ovarian cancer annually in the United States. Unfortunately, ovarian carcinoma frequently is not detected until it has spread outside the ovary; consequently about two-thirds of women with this malignancy succumb to the disease. The tumor suppressor research may provide new treatment and prevention modalities for ovarian cancer.

Metastasis, the primary cause of death in cancer, is a complex biological process. A series of discrete steps permits tumor cells to leave the primary site and establish new tumor growth in distant organs. These steps include: growth of the primary tumor, invasion of the membrane separating the epithelium from the underlying tissue, entry into and exit from blood vessels, invasion and new growth at the distant site. Many genes are clearly involved in this process.

Important research this past year has shown that aggressive tumor cells lack certain proteins which normally suppress invasion and metastasis. In non-cancerous cells these suppressor proteins regulate communication between cells and control tissue structure. Thus, a malignant tumor cell is metastatic because it has an imbalance of properties, either an elevation of invasive factors or a loss of suppressor factors.

A new development in metastasis research is the isolation of suppressor genes which block metastases by certain tumors. The first metastasis suppressor gene is called NM23. The insertion of NM23 into mouse tumor cells blocks metastases in the test animals. NM23 appears to function in normal cells to regulate growth and tissue pattern formation by regulating cell-cell communication. Loss of NM23 is strongly associated with poor survival in human breast cancer. NM23 thus offers a new approach for possible gene therapy of breast cancer. Intensive studies are being conducted in this area.

TUMOR BIOLOGY AND IMMUNOLOGY

The Immunology Program at the NCI continues to vigorously explore the diverse ways the immune system acts to control the growth of tumors. Studies focus on genetics, biochemistry, cell biology and immunology. The development of vaccines for the primary or secondary prevention of cancer is a major goal of the National Cancer Institute. Cancer is very different from infectious diseases and the development of cancer vaccines requires additional knowledge and the application of new concepts in immunology.

There are major emphases in four areas of research in cancer immunology relevant to vaccines: the ability of the T lymphocyte to recognize a tumor cell as "abnormal;" the study of a pair of molecules called CD4 and CD8 on the surface of T lymphocytes; the analysis of the lymphokines, the

immunoregulatory molecules produced by cells of the immune system; and issues relevant to the vaccine effort such as immune suppression and tolerance. Understanding these components will enable the development of cancer vaccines.

A critical discovery in immunology, central to the development of cancer vaccines, is the way in which an antigen is recognized by T lymphocytes. This question has now been answered in large part enabling progress in analyzing cellular recognition of tumors and other complex antigens, and the effective methods to therapeutically stimulate those reactions.

Basic studies of antigen recognition in mice have generated other approaches for tumor control. A class of superantigens has been discovered, each capable of stimulating a large subset of T cells. Some superantigens are bacterial toxins and some are the products of integrated tumor viruses in the mice. If superantigens can be isolated from human cell lines, they may represent a significant new vaccine potential.

In addition to a strong emphasis on cancer vaccines, NCI is supporting research for the development of monoclonal antibodies for the treatment and diagnosis of cancer, and a new program to study the immunobiology of breast cancer. Much has been discovered regarding the role of oncogenes, hormones, and other growth factors in the development of breast cancer. At present, little is known about the tumor's interaction with the immune system and its importance in the pathogenesis of the disease. To maximize the contribution the immune system can make to breast cancer control, NCI has launched new efforts to delineate the mechanisms of host immune system rejections of breast tumors.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS, caused by infection with the retrovirus known as Human Immunodeficiency Virus (HIV), was recognized in 1981 and has now become a global pandemic. NCI has made major contributions to the basic understanding and therapeutic management of all stages of HIV infection. NCI investigations have been conducted in full cooperation with the National Institute of Allergy and Infectious Diseases (NIAID), and other agencies of the government.

HIV attacks the immune system, and inserts its DNA into the white blood cells. The primary target cell for HIV is the CD4-positive T lymphocyte. Following infection, the HIV genome further subverts the cell by utilizing cellular machinery that normally regulates genes involved in the immune system.

This past year, NCI investigators developed a new sensitive assay which makes it possible to detect exposure to HIV antigens before the individual's sera becomes positive for HIV antibodies, and also before the virus can be detected in the blood by the earlier polymerase chain reaction (PCR) assay.

Kaposi's Sarcoma was one of the earliest recognized manifestations of AIDS. Certain lymphocytic cancers, primarily non-Hodgkin's lymphoma, are also found in AIDS patients. Recent documentation indicates an increase in the incidence of lymphomas in the population. This is largely attributable to the rapidly

rising incidence associated with AIDS. Lymphomas have become a major clinical problem in AIDS patients.

To better understand the causes of lymphoma, basic scientists have recently developed animal models of lymphoma. Clinical researchers are now analyzing the lymphomas found in AIDS patients. They occur in sites other than lymph nodes, including the central nervous system, gastrointestinal tract, lungs, jaws, etc. It has been postulated that additional viruses are the cause of AIDS-associated lymphomas, or may be involved as necessary secondary factors.

Epstein-Barr Virus (EBV) is known to be a factor in African Burkitt's lymphoma, and, therefore, AIDS patients with lymphomas were analyzed for the presence of EBV. EBV was found to be present in at least 50 percent of all cases. These studies continue at a number of NCI-supported laboratories.

A major public health priority is the development of a safe and efficient AIDS vaccine to decrease mortality from AIDS and AIDS-related malignancies and ultimately to prevent HIV infections. Traditional approaches to vaccine development using killed or live-attenuated virus do not elicit strong responses. These vaccines also present potential safety problems due to the extreme variability found in HIV.

The NCI AIDS Vaccine Program at the Frederick Cancer Research and Development Center (FCRDC) is purifying and analyzing subunits of the virus and assessing prototype vaccines in chimpanzees. Over 500 vials of a national reference stock of infectious HIV-1(MN) have been prepared for use as a virus challenge in immunized chimpanzees. The production and purification of HIV-1(MN) also provides material for viral protein purifications for use in the preparation of non-infectious HIV mutants and for immunoassay development.

NCI scientists have recently identified several major peptide segments of HIV proteins that induce immune system responses, making these peptides good candidates for a synthetic vaccine. The design of an effective synthetic vaccine is being intensively pursued at NCI.

The development of new anti-HIV drugs is a high priority for the NCI. Since 1987, almost 50,000 agents have been screened (over 23,000 synthetic compounds and over 24,000 natural products). Of these, 416 have shown positive activity. Fewer than one percent will be clinically useful because evaluations of toxicity and efficacy will preclude most from full scale development.

Following identification of <u>in vitro</u> anti-HIV activity, the most promising drugs undergo preclinical drug development. Two important new drugs being studied are fluoro-dideoxycytosine (F-ddC), and oxathiin carboxanilide. It is expected that clinical trials with these compounds will begin this coming year.

In pediatric AIDS, trials of F-ddC and a new reverse transcriptase inhibitor are being initiated. The NCI Pediatrics Branch has emerged as an important and productive center for generating new knowledge about treating childhood AIDS.

<u>CONCLUSIONS:</u>

The National Cancer Program is a highly significant, productive biomedical research enterprise. The special authorities provided by the National Cancer Act have proven their value. The National Cancer Act provided a system of Presidentially-appointed advisory bodies to ensure vigorous oversight and open debate of major programs. The resulting progress is apparent in the hospitals and homes of this nation, where the benefits of the past two decades are evident.

Over 500,000 people did die of cancer in 1991. One of every five deaths in the nation is due to cancer. However, seven million living Americans have been cancer patients, and over three million of these have lived at least 5 years since their diagnosis. These statistics were not possible to achieve 20 or 10 years ago. They have become possible because of basic research findings and advances in treatment modalities.

Much remains to be done. We must prevent the start of cancer, which each year appears in over one million Americans. We must learn how to better treat

cancer in those over 65 years of age, where death from cancer is the highest, and we must work most diligently to help our poorest populations.

The National Cancer Institute has initiated specific programs targeted to poor adults and to poor children. New initiatives in all these areas must continue to be developed with continuing vigorous support from the government. This is a crucial need of our nation's citizens.

Harold P. Freeman
Chairman

NATIONAL CANCER INSTITUTE

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