

INTEGRATIVE ONCOLOGY: CANCER CARE FOR THE NEXT MILLENIUM

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Good afternoon. I am Dr. Robert Wittes, Deputy Director of Extramural Science and Director of the Division of Cancer Treatment and Diagnosis, the National Cancer Institute (NCI), National Institutes of Health (NIH). Accompanying me today is Dr. Jeffrey White, Director of NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM).

I am pleased to be invited to address the House Government and Reform Committee today to report on our progress in the fight against cancer and to discuss the future of cancer care in the new millenium. With the help of new advanced technologies we are entering the next decade in this new century with the ability to unlock critical information about the nature of cancer - what we know now to be a class of over 100 different diseases that share certain features. Because of this fact, it is unlikely that one magic bullet will solve the problem.

Many of us - scientists, health professionals, and health care providers - have devoted our careers to finding cures, and treating, and caring for the cancer patient. The network of concerned citizens is vast - from the community volunteer who drives a cancer patient to chemotherapy, to the cancer survivor who devotes his/her time to offer hope to others. We have seen our share of family members, friends, and patients lose their fight to cancer as we struggle to save them - to find the cure. Our losses, albeit painful, just intensify our resolve to find a cure - to stop the suffering it causes. Each year, we are seeing 1.2 million new cancer cases, and at least a half million cancer-related deaths.

But, as a nation, we are beginning to see results from our investment in cancer research. I am pleased we are able to report that cancer mortality continues to decline. The rate of new cancer cases and deaths for all cancers combined as well as for most of the top 10 cancer sites declined between 1990 and 1997. Drops continue to be seen for the four major cancer sites of lung, colorectal, breast and prostate. Overall, mortality rate drops are seen in both the black and white population. Remarkably, the magnitude of these drops are such that, for the first time, between 1996 and 1997, the total number of cancer deaths did not rise, despite a population that is growing and aging.

According to the most recent report from the NCI's Surveillance, Epidemiology and End Results (SEER) Cancer Registry Program, survival for children with cancer has improved dramatically since the early 1960s, when fewer than 10% of children with leukemia survived and when only 28% of all children with cancer were alive five years from their diagnosis. Today, over 80% of children with acute lymphoblastic leukemia (ALL) are surviving five years from diagnosis, with most of these children cured of their leukemia. Overall survival rates for children with cancer have increased to 75%.

Corresponding to improvements in survival rates have been substantial decreases in childhood cancer mortality, with the mortality rate decreasing nearly three-fold from 1960 (~80 per million) to 1997 (~25 per million). For specific cancer types such as leukemia and non-Hodgkin's lymphoma, there have been four to five fold decreases in mortality rates.

As most children with these diagnoses are treated in clinical trials conducted by the NCI-supported clinical trials cooperative groups, the improvements described above and illustrated in the attached figures largely reflect advances in therapy identified in these clinical trials.

Recent advances identified in NCI-sponsored clinical trials that have contributed to increasing survival rates include identification of the following improvements in treatment:

- Cis-retinoic acid, which is related to vitamin A, given following completion of high-dose chemotherapy and autologous bone marrow transplantation, improves outcome for children with high-risk neuroblastoma.
- Dexamethasone is more effective than prednisone for children with "standard risk" ALL.
- Intensive asparaginase treatment is important for favorable outcome for T-cell ALL.
- Wilms' tumor can be successfully treated with an intensive administration of chemotherapy over just 6 months, a much shorter period than for the previous standard chemotherapy regimen which was given over 15 months.

Despite the advances over the past 40 years, there remain approximately 1,500 children younger than 15 years of age and an additional 700 15-19 year olds who die of cancer

each year in the United States. Only when all children are free from the threat of cancer can we be satisfied with our progress.

For adult cancers, the SEER report indicates that, by far, the greatest decline in cancer incidence rates has been among men, who, overall, have higher rates of cancer than women. Yet, certain recent trends threaten to undermine the progress we have made. The incidence of melanoma, an aggressive skin cancer, has been rising about 3% per year, although death rates have remained constant, and incidence rates for non-Hodgkin's lymphoma continue, inexplicably, to rise.

In addition, adolescents are now smoking and using tobacco products – a major risk factor for lung and other cancers – at a troubling rate, which may well reverse the currently falling rates of lung cancer in coming years.

Moreover, we are aware that the burden of cancer is not equally experienced across our population - that certain racial, ethnic, and socioeconomic groups continue to be disproportionately burdened by cancer. Monitoring rates and trends over time, by geography, by gender, age and racial and ethnic groups has been a priority for the NCI and we are particularly concerned about the disproportionate impact of cancer on the poor, the medically underserved and certain ethnic groups. We are committed to discovering the reasons why cancer disproportionately affects specific populations.

We know that appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of disease. NCI uses data from SEER to identify and study trends, track the impact of cancer on the general population, and provide information to help researchers find out why certain populations are affected by cancer more severely than others. However, recent changes in health care financing and delivery, the revolution in informatics and computer programming technology, and the social and cultural diversity of our country present new challenges and opportunities in surveillance research. We plan to expand our data collection to include patterns of cancer care, as well as treatment and quality of life outcomes. In addition, new investments are planned to find tools that will improve the precision and expand the reach of cancer surveillance, and to encompass a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. Greater efforts are also planned to disseminate the results of NCI's surveillance research.

In his recent testimony before the House Appropriations Committee, Dr. Klausner, Director of the NCI, outlined a number of expansions in our programs aimed at the ability to assess, explain and affect the unequal burden of cancer. These expanded and new initiatives address the important message of last year's Institute of Medicine (IOM) report on the unequal burden of cancer. These new initiatives include:

NCI will expand the SEER Program to include populations with differential cancer rates that are currently under-represented (e.g., Non-Mexican Hispanics, rural African Americans, American Indians, high poverty, and high cancer death rates). Expansion will strengthen the existing national infrastructure for surveillance research, which in turn will

improve understanding of health disparities in cancer outcomes among major ethnic populations, including rural whites and blacks, non-Mexican Hispanics and Native Americans.

We have signed a new Memorandum of Understanding (MOU) with the Centers for Disease Control and Prevention (CDC) to formalize collaboration and integration of the NCI's surveillance and surveillance research programs with the CDC's National Program of Cancer Registries. This will allow a strategic integration of the NCI's more intensive surveillance and research system with the CDC-funded state registry systems, to help develop data standards and tools for pooling data.

This year we have funded a new research program of Special Population Networks (SPNs) for cancer control and research. These new consortia will be based within various communities serving different segments of our diverse society in order to establish cancer control and research infrastructures to work within and to serve these communities. To support the activities of these SPNs, we are establishing a cancer control academy at the NCI for training and will link these community-based research networks to the full range of information and communication resources of the NCI. These SPNs, we hope, will provide the basis for a new national platform for cancer research to address the distinct cancer burdens of special populations. We are setting aside \$50-60 million over five years to fund about 17 SPNs (\$12 million in FY 2000), the largest program of its kind we have ever funded.

This year, in collaboration with the NIH Office of Research on Minority Health, we began funding five research partnerships between NCI-designated cancer centers and minority institutions to create active and successful academic research programs linked to our most successful cancer research institutions. We plan to release a new Request for Applications (RFA) to sustain and enhance these new enterprises. A more complete description of our activities in this crucial area can be found at the NCI Office of Special Populations Research Web site.

Monitoring cancer incidence and mortality trends can help us formulate questions about the distribution of cancer control and care, as well as about possible causes of cancer. This year, the NCI released, for the second time in its history, 25-year cancer mortality maps. These cover all 3,100 United States counties and state economic areas, for 40 cancer sites, by gender and race. These maps are available on the NCI Web site in a user-friendly and dynamic format. They do not tell us causes of cancer or indeed whether a geographic pattern reveals either a localized environmental factor, a behavioral pattern or a socio-economic pattern. But, by providing the starting point for addressing these issues, these maps are crucial resources. The NCI will release a Request for Application (RFA) to support two types of studies linked to these maps: epidemiologic research to search for explanations for geographic and temporal cancer patterns, and methodologic research to develop Geographic Information Systems (GIS) for evaluating environmental associations with cancer. These maps are one part of NCI's extensive program in establishing environmental (exogenous) causes of cancer.

Recent Advances in Cancer Research

Progress in our understanding of the biology of cancer continues at an astonishing pace. We are learning more each day about how cancer arises from a single cell that behaves abnormally, dividing uncontrollably and leading, eventually, to the development of a tumor. We also are learning about the ways that genes, which direct the behavior of the cell, interact with a host of environmental agents to cause cellular malfunction and disease. This basic knowledge about the nature of cancer is providing us with critical insights into how we can prevent and detect cancer more effectively. And it is giving us the opportunity to improve treatment by enabling us to design therapies that target the machinery of the cancer cell. Powerful new technologies are permitting us to detect and diagnose cancer at an earlier stage, before it has had the chance to spread. People with cancer are living longer, and with a better quality of life, than ever before.

Altered genes and molecular pathways in a cell are already providing long-sought targets for new therapeutics. Identifying the specific molecular pathways that define each type of human cancer has allowed us to begin to replicate these changes in the genes of mice. These mice develop cancer that more accurately mimics human cancer. This will allow the development of mouse models of human cancer that more accurately predict the behavior of human disease and response to treatment than mouse models previously available.

The knowledge that cancer cells develop by changing their molecular profile has set the stage for a new and systematic approach to both early detection and accurate diagnosis. Three years ago, the NCI set out to establish a full index of all the genes that are altered in each type of cancer. This project, called the Cancer Genome Anatomy Project or CGAP, has been extremely successful, identifying tags for the vast majority of human genes, annotating what types of cells and cancers express those genes, developing catalogues of chromosomal changes in cancer and discovering common genetic variations that will help to explain why individuals are different in their risk of getting cancer, their sensitivity to diet and the environment and their response to therapy. CGAP has become one of the most widely used sources of information and reagents in the research world. Systematic gene discovery through CGAP and other projects is about to profoundly change our approach to the classification, and therefore the accurate diagnosis of, cancer.

For the past three years, the NCI has been redirecting its drug discovery program to one based on the success of basic research in identifying the precise molecular targets implicated in the development, growth, and spread of cancer. The preventive agents and therapeutics of the future will be aimed at these targets.

The recent encouraging results of Herceptin for the treatment of advanced breast cancer, Rituximab for the treatment of non-Hodgkin's lymphoma, STI 571 for the treatment of leukemia, tamoxifen for reducing the risk of breast cancer and a growing list of others, all point to the future face of molecularly targeted therapeutics and preventives. We have funded six new centers to develop new libraries of chemical diversity and test them

against promising molecular targets. This year, we will fund an ambitious new Molecular Target Drug Development Discovery Program aiming at the validation of molecular targets that derive from advances in cancer biology.

Historically, natural products -chemicals derived from plants and microorganisms - have been a fertile source of new compounds for cancer and other areas of medicine. NCI is currently considering ways to enhance our activities in natural products drug discovery and to make our internal capabilities in natural products isolation and identification available to research groups throughout the country that are engaged in the search for new cancer preventives and therapeutics.

Last year, we initiated a novel program called RAID (Rapid Access to Intervention Development) that evaluates promising drug candidates in the laboratories of academic investigators and, via peer review, manages the movement of these candidate drugs from the lab to the point of clinical trial. To date, 35 novel agents have entered the RAID pipeline and in one year four have reached or are ready for clinical trials. We will expand this successful program in the coming year.

NCI's Challenge: Building the Capacity of the Future

Our capacity to build on our recent accomplishments is critical to further progress against cancer. First, we must sustain and strengthen the research programs that have enabled us to pursue a path of scientific excellence and discovery in cancer research, providing opportunities for researchers to explore new, innovative, and unconventional ideas, including complementary and alternative medicine (CAM), to make new discoveries in cancer research.

Second, we must seize extraordinary scientific opportunities made possible by advances in science and technology. Through expanded support for investigator- initiated research, by strengthening the integration of cancer research centers, and by supporting the expansion and integration of networks and consortia to spur creativity and to explore new and innovative ways to detect, diagnose, treat, and prevent cancer, we expect to strengthen the cancer research infrastructure and enable basic discovery to rapidly improve clinical practice.

Third, we are committed to strengthening the National Clinical Trials Program. In the past two years, the results of clinical trials have set new standards for increasing the effectiveness and reducing the toxicity of regimens for childhood cancers, leukemia, myeloma, breast cancer, ductal carcinoma in situ (DCIS), cervical cancer, head and neck cancer, lymphoma, colorectal cancer, prostate cancer and others. To sustain these efforts NCI is extensively restructuring our national clinical trials system. We want to improve the quality of scientific questions asked, increase speed and efficiency and decrease the administrative burdens of participating in clinical trials. Furthermore, we want physicians and patients to have access to the full menu of available clinical trials. Currently, about 20,000 new patients are enrolled annually in NCI-sponsored treatment trials. We want to make certain that our clinical trials system is able to keep pace with the dramatic increase

in the number of new therapeutic and preventive agents that warrant testing. Many more patient-volunteers are needed to help establish the benefits of new agents, new combination treatments, and complementary and alternative cancer therapies. Our planned enhancement of the infrastructure to support these studies will be critical.

Fourth, the power of computer-based communications and the World Wide Web are making possible unprecedented research opportunities. Paper-based research systems are giving way rapidly to integrated systems that share information and knowledge effortlessly and enable new discoveries to be made at the researcher's desk, not just in the lab. A strong cancer informatics infrastructure is vital to NCI's efforts to foster collaboration among the conventional and CAM communities by helping to speed the discovery process, translate the best discoveries into clinical trials, and transform cancer care through more effective and efficient information exchanges.

Fifth, as I described previously, the expansion of NCI's cancer surveillance efforts is vital to our efforts to prevent and control cancer. Through the planned efforts I have included in my written testimony, NCI continues to play an active role in developing a comprehensive national surveillance program.

Finally, new ways of educating, training, and developing scientists are necessary to ensure that technology advances are integrated rapidly into the cancer research enterprise and that scientists are prepared to work together in team settings to unravel the complex factors contributing to human cancer.

NCI Progress in Complementary and Alternative Medicine (CAM)

Since Dr. Klausner addressed the Committee in 1998 and outlined NCI's goals to strengthen NCI's role in CAM research, much progress has been made. I am pleased to report that we have not only met those goals but surpassed them. NCI is supporting a number of high quality CAM-related research projects, including projects examining the effects of dietary interventions in cancer treatment, projects examining the therapeutic value of vitamins and minerals in cancer prevention and treatment, studies in stress and pain management to enhance the quality of life for cancer patients, and studies examining the effect of natural inhibitors of carcinogenesis. We are working closely with the NIH National Center on Complementary and Alternative Medicine (NCCAM), under the leadership of my colleague, Dr. Straus, to encourage the conventional cancer research community to initiate new CAM research studies at NCI-sponsored cancer centers. In addition, as Dr. Straus mentions in his testimony, NCCAM and NCI are initiating a new research grant mechanism - Quick Trials for Novel Cancer Therapies - to ensure timely development of new treatments.

The NCI is extremely pleased with the support and guidance Dr. Straus and his staff have provided the Institute in our efforts to strengthen the integration of cancer-related CAM research into the cancer research agenda. Through the leadership of Dr. Jeffrey White, NCI is actively involved in forging collaborative relationships between the conventional

cancer research and CAM communities, and progress has been made in strengthening the Institute's relationship with CAM researchers and practitioners.

NCI has made progress in incorporating CAM information into NCI's cancer communications network. Of considerable importance to all of us is the public availability of accurate, up-to-date information about CAM therapies. NCI has taken steps to assure that this information receives the same consideration as conventional approaches in our evaluation and dissemination efforts. Few health-related interventions have the potential of interactive health communications to improve health outcomes, decrease costs, and enhance consumer satisfaction. Indeed, effective communication is central to cancer care, from primary prevention through survivorship.

Detailed CAM summaries have been prepared for cancer therapies identified by our Cancer Information Service and the NCCAM Clearinghouse as being of public interest. The continued development of these and other CAM-related summaries will follow the same model as those for conventional therapies and include specific trial results and references to the published literature. They will be reviewed by the appropriate Physicians Data Query (PDQ) Editorial Board depending on whether the intervention is for the treatment or prevention of cancer or used as a supportive care intervention. In addition, these summaries will be sent to experts in the CAM community for review and comment before they are made available on the NCI web site.

Information Dissemination Efforts

NCI has moved rapidly to expand linkages to CAM-related cancer information throughout our existing cancer information network. In addition, NCI has developed CAM Cancer PDQ Summaries and Cancer Fact Sheets on a number of CAM therapies. CAM-sensitive and knowledgeable reviewers participate in the review of these summaries, and once approved by NCI's Physician's Data Query (PDQ) Editorial Board, are put on the NCI website. New summaries are planned to be completed and fully reviewed quarterly. An updated list of CAM Fact Sheets and PDQ CAM summaries currently on the NCI Website is included in my written testimony. These summaries can be found at website address: <http://cancernet.nci.nih.gov/treatment/cam.shtml>

They include Cancer Fact sheets on Cancell, Gerson Therapy, Immuno-augmentative Therapy, Laetrile, the NCI-Sponsored Clinical Trials of Antineoplastons, and NCI Studies of Hydrazine Sulfate. Also currently available are PDQ summaries on Hydrazine Sulfate, Laetrile, and Cartilage (Bovine and Shark). Green Tea is one of the topics for an upcoming PDQ summary, and other summaries have been drafted and are ready for review. They include: 714-X, Mistletoe, and Coenzyme Q10.

Through collaborative efforts with NCCAM, NCI has expanded its commitment to develop new centers for CAM research, and to support research to evaluate the efficacy of intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support in the treatment of inoperable adenocarcinoma of the pancreas. The NCI has collaborated with the NCCAM to begin a randomized, prospective evaluation of Dr. Nicholas

Gonzalez's therapy (a nutritional program with oral pancreatic enzymes and a "detoxification" regimen) at Columbia Presbyterian Medical Center, one of the NCI-designated Cancer Centers.

Because of public interest in the potential anti-cancer activity of shark cartilage and its continued use despite the lack of persuasive clinical evidence of efficacy, the NCI is collaborating with NCCAM to sponsor clinical trials in this area. The first trial is with the Canadian company (Aeterna). This trial is centered at the MD Anderson Cancer Center's Community Clinical Oncology Program with accrual sites in the U.S. and Canada. The study is a phase III randomized study in patients with non-small cell lung cancer. Both arms of the trial will receive standard therapy (chemotherapy + radiation therapy), one arm will receive the liquid shark cartilage product and the other study will receive a placebo. The first patients are currently being entered onto this study. A second shark cartilage trial is planned to be centered at Mayo Clinic in conjunction with the North Central Cancer Clinical Trials Group. NCI staff in the Division of Cancer Prevention have been instrumental in establishing phase I and II clinical trial protocols using formulations of the active components from green tea. These clinical trials began accruing patients in December 1999.

As a result of efforts to encourage NCI's intramural community to explore CAM research, we are seeing intramural researchers at NCI involved in examining the use of alternative medical therapies in adult cancer patients enrolled in Phase I clinical trials, and the use of complementary or alternative medicine practices by women at increased risk for breast cancer. NCI intramural researchers are also conducting a Phase I randomized study of Genistein, a soy product, for prevention of cancer in patients with no history of cancer or with asymptomatic early prostate cancer or other malignancy.

The Cancer Advisory Panel for Complementary and Alternative Medicine (CAPCAM), an expert panel that provides advice to both NCCAM and the NCI, is actively evaluating applications elicited from the CAM community by NCI's Best Case Series Program. As a result of CAPCAM recommendations, NCI is exploring the possibility of prospective outcomes monitoring on new lung cancer patients treated in a homeopathic clinic in India. Dr. White is working with the P Banerji Homeopathic Research Foundation clinic in Calcutta, to explore onsite monitoring of new lung cancer patients seen in the Banerji's clinics and to obtain the documentation and follow-up of a group of 30 - 50 new lung cancer patients for a period of 12 - 18 months.

NCI has also evaluated results of "Sun soup" clinical experience in lung cancer. This small uncontrolled trial that uses an herbal supplement in the treatment of lung cancer was presented to the CAPCAM in July, 1999. Dr. Alexander Sun, the originator of the "Sun soup" product, is applying for a research grant to support further clinical study.

The NCI continues to review CAM modalities for research readiness. This is an ongoing process of surveillance of the field to identify areas of research opportunity. This process will allow the identification of modalities appropriate for grant or contract support.

CAM Cancer Information Program

In February, 1999, NCI established the Cancer CAM Research Interest Group. This group is the only continuous and open forum for members of the NIH community to learn about and discuss the current status and potentials of CAM research as it relates to the treatment of cancer patients. This group allows for more frequent opportunities for productive interchange between the alternative and conventional medical and research communities. Topics of discussion may include: lectures from outside speakers about various aspects of and types of CAM or CAM-like research or clinical practice, discussions of comprehensive literature summaries, updates of ongoing CAM cancer research, and identification of opportunities for intramural and extramural research in CAM or CAM-related areas. Further, NCI continues to sponsor lectures and seminars on a variety of CAM-related topics.

We are also pleased to report that a website for the NCI Office of Cancer Complementary and Alternative Medicine has just been launched (<http://occam.nci.nih.gov/>). The site will be used to communicate with the general public and extramural research and practice communities as well as intramural NCI and NIH program and administrative staff. It will contain updates and status of current and planned NCI CAM projects and will serve to project a visible research agenda and to make more transparent the NCI's processes for handling CAM issues (e.g. the Best Case Series Program).

The NCI is currently embarking on a project to develop a cancer-related CAM Citation Database to augment the cancer component of the existing NCCAM CAM Citation Index. This database will become a resource for NIH and extramural investigators interested in CAM research and will include articles and abstracts from many databases including Medline. The database will serve as a resource for NIH and extramural investigators interested in CAM research.

Conclusion

Again, thank you for inviting me to address you today. I look forward to discussing NCI's contributions to the scientific body of knowledge needed to support efforts to integrate complementary and alternative medicine into cancer care in the new millenium. Through the careful application of research and discovery, the 21st century can and will be the era in which cancer finally is conquered.