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BLOOD CANCERS

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS
UNITED STATES SENATE

ONE HUNDRED SEVENTH CONGRESS

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[1] Committee and subcommittee memberships—June 6, 2001 to July 10, 2001. Senate committee and subcommittee assignments reverted to that which had been in existence at the conclusion of the 106th Congress.

NOTE.—From January 3 to January 20, 2001 the Democrats held the majority, thanks to the deciding vote of outgoing Democratic Vice President Al Gore. Senator Thomas A. Daschle became majority leader at that time. Starting January 20, 2001, the incoming Republican Vice President Richard Cheney held the deciding vote, giving the majority to the Republicans. Senator Trent Lott resumed his position as majority leader. On May 24, 2001, Senator James Jeffords of Vermont announced his switch from Republican to Independent status, effective June 6, 2001. Jeffords announced that he would caucus with the Democrats, changing control of the evenly divided Senate from the Republicans to the Democrats. Senator Thomas A. Daschle became majority leader once again on June 6, 2001.

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BLOOD CANCERS

THURSDAY, JUNE 21, 2001

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN
SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:35 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Tom Harkin presiding.

Present: Senators Harkin, Murray, Specter, Stevens, and Hutchison.

Also present: Senator Mikulski.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Good morning and welcome to today's subcommittee hearing on blood cancers.

Before I begin, my staff has informed me we have about 300 people lined up in the hallway outside. This was the only hearing room that we could obtain today, and as you know, it is very cramped for space. So, if I could ask everyone to please have a seat. If we have extra spaces, we will be able to let some more people in.

Also, I would like to ask for your indulgence. If you are here on a panel and you are here to listen to a certain panel, if after that panel is finished, if you would be so kind as to perhaps remove yourself from the room and let others come in. There are a lot of people out there who would like to come in and participate in this hearing. So, I would just ask if you could do that, I know there are a lot of people out there who would really appreciate it, and I would appreciate that.

This is my first hearing as chairman since 1994, and I would like to start first by thanking Senator Specter for the tremendous work he has done over the past 6 years.

Right now there is a vote on the Senate floor. I think it started at 9:30. I will make my opening statement and proceed, and then as soon as Senator Specter shows up, I will leave to go vote and then he will chair the hearing.

But even in his absence, I want to say that he and I have switched back and forth between chairman and ranking member since 1989, and we have been partners every step of the way.

I remember back in the early days when everyone thought we were crazy for wanting to double the NIH budget within 5 years. Now we are halfway to that goal, thanks in large part to our bipartisan teamwork.

Senator Specter and I have also worked together on education, worker rights, stem cell research, and many other important issues. That is not going to change just because I am the chairman now and he is the ranking member. He will continue to be a leader on the subcommittee and I will continue to seek his advice and support and friendship for years to come.

So, I publicly want to applaud Senator Specter for his leadership on this committee and for working so closely with me over the years.

Today's hearing is on the important subject of blood cancers: leukemia, lymphoma, and multiple myeloma.

Seeing everyone gathered here this morning and the 300 out in the hall reminds me how far we have come since the days when people were afraid to even say the word "cancer." Today we are not only discussing these diseases openly, but we are celebrating some remarkable advances in fighting them.

Just last month, the FDA approved what is perhaps the most promising cancer drug ever developed. This drug called Gleevec was given to 54 patients with chronic myeloid leukemia. In 53 of those patients, the disease basically disappeared. A year later, 51 had a normal blood count.

One reason this is so exciting is it is the first FDA-approved drug that directly turns off the signal of a protein known to cause cancer. Many researchers believe it marks a new era in the war against this disease.

We are also learning more about the use of thalidomide in treating multiple myeloma. Those of us who remember the devastating birth defects caused by thalidomide in the 1950's might find it hard to believe that the drug could stave off cancer, but that does seem to be the case.

Much work remains to be done. That is one reason why the members of this subcommittee are fighting so hard to raise the funding for the NIH, to find better treatments and cures for diseases like leukemia, lymphoma, and multiple myeloma.

We are fortunate to have a distinguished panel of guests with us this morning to discuss blood cancers. I would like to personally extend a special welcome to Dr. Sandra Horning, Professor of Medicine at Stanford University School of Medicine. Dr. Horning is a native of Creston, Iowa, right in my back yard, and she earned her B.A. and M.D. from the University of Iowa. So, I am particularly proud of the work that she is doing on lymphoma.

I also want to thank Geraldine Ferraro, a long-time friend and coworker of mine in the House of Representatives, a leader in my party, and I think a leader for a lot of us throughout the Nation. I want to thank her for being here this morning. Ms. Ferraro has been a trailblazer her whole life; first, of course, in Government and politics, and now as an advocate for medical research. All of us were saddened to learn about her multiple myeloma, but we are grateful that she has decided to speak out about her experiences.

I want to recognize some other Iowans who are here today: Scott Smith of WOI TV, Catherine Rhoda, a patient advocate, and her husband John, Dr. George Weiner, a researcher at the University of Iowa. And I want to thank all of you for making the trip to Washington to be with us this morning.

STATEMENT OF RICHARD KLAUSNER, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator HARKIN. We will first start off with a long-time friend and a great leader in our battle against cancer. Dr. Richard Klausner was appointed Director for the NCI in 1995. Previously he served as Chief of the Cell Biology and Metabolism Branch of the National Institute of Child Health and Human Development. He began his career at NIH in 1979 after post-graduate work at Harvard. He received his undergraduate degree from Yale and his medical degree from Duke University.

Dr. Klausner, I personally want to thank you for your tremendous leadership at the National Cancer Institute and for all of your willingness to keep us briefed and up to date on everything. Welcome again this morning, and please proceed.

Dr. KLAUSNER. Thank you, Mr. Chairman. I want to thank you and the committee for holding this hearing on leukemia, lymphoma, and myeloma. These are a very complex and extremely diverse set of dozens of different diseases whose overall burden is immense. Currently there are about 700,000 Americans alive who have received the diagnosis of one of the three classes of diseases. One hundred thousand new cases will be diagnosed this year, and 60,000 Americans will succumb to one of these diseases this year.

These diseases have long been at the forefront of oncology, or cancer research, in terms of basic science, clinical research and application, and progress in these diseases mirrors the ups and downs, the highs and lows of the history of cancer research. For some diseases, we can now achieve 80 to 90 percent cure rates whereas, in others, the ability to effect cure is rare.

What I want to do briefly this morning is show you some of the directions where we are going, as you and I have talked about quite a lot over the last 5 or 6 years. But before I do that, let me just describe a little bit of what these diseases are. As you said, these are diseases of the cells that make up the immune and the blood systems.

All of these cells arise from a multi-potential stem cell that goes through a very complex, specific pattern of changing, of development, to differentiating so that they become the dozens of specialized cells of the immune and blood systems.

This is important because each different disease is defined by two things: one, what type of specialized cell this cancer arises in; and two, the type of DNA or genetic alteration that results in that type of cell going from a normal cell to a cancer cell.

Now, critical to the theme of how we are going to approach successful prevention and treatment of these diseases, for all cancers, is to understand their causes and to better define them. I have some posters here to illustrate. These diseases really are many different diseases. Often we misclassify these diseases by giving them the same name. This is a problem. We need to be able to move to precise and definitive ways of defining and diagnosing each cancer, knowing what is wrong in each of them, and then targeting our therapy to what is wrong.

Let me show you one example in lymphoma. I know this may be a little hard to read, but there is one particular type of lymphoma

called diffuse large cell lymphoma. We have developed therapies, combination chemotherapy, that will cure about 45 percent of patients. The question is why 45 percent? One possibility is that this is not one disease. And as I have presented to this committee before, advances in technology, genomics, and molecular biology have allowed us to rethink our fundamental approach to classification of these diseases.

On this first poster is some very new information that shows when we use a new technology called DNA chips, which we have talked about before, this single disease, a disease that we had a single name for just a year ago, is at least two diseases. Perhaps most strikingly, when we now look at the ability to cure patients with these two diseases, we can see that one type of disease can be cured over 80 percent of the time and the other type of disease can rarely be cured. This is the type of change in our approach that is going to guide how we are going to develop new therapies.

Now let me briefly run through a few of these new therapies and a few of our new approaches.

NEW THERAPIES

Senator Harkin described this new drug Gleevec that targets the molecular machine responsible for a particular form or leukemia, chronic myelogenous leukemia. It is also present in some other cancers. This is a drug that stops or shuts off the molecular machine that causes this cancer. As Senator Harkin said, over 90 percent of patients with CML treated with this single oral drug have gone into complete and sustained remission.

On the next poster we can see an example of targeting the immune system itself against some of these diseases. This represents a study being done in Bethesda at the National Cancer Institute that has found a particular molecular target that is present on particular forms of leukemia, in this case a type of leukemia called hairy cell leukemia. This has led to the creation of a new molecular drug that has the specificity of an antibody and which is linked to a very toxic compound from a bacteria. This toxin, a single molecule of which gets into a cell, is sufficient to kill the cell, and this is now being used against hairy cell leukemia. In the original results, in patients for whom all other treatments had failed, over 90 percent have gone into complete and sustained remission.

The next example is another immunologic approach where we are learning how to actually raise vaccines to vaccinate an individual against their own cancer. This looks particularly promising in these sorts of malignancies. In this case, in a trial headed again by an NCI investigator, Dr. Kwak, looking at a type of lymphoma for which we have no definitive treatment, what he has seen is about 85 percent of patients in whom an immune response can be raised against their cancers go into complete and sustained remission, something we have never seen before. This remission is not only a complete clinical remission, but we cannot even detect with our most sensitive molecular measures that any of the disease is there.

As we heard before, myeloma has been an extremely difficult disease to make progress against. But recently an old drug, thalidomide, an infamous drug from a generation ago, was recognized to

inhibit blood vessel formation, and in fact, this is the first drug that is showing some significant and encouraging responses in about 30 percent of patients with myeloma. There is a lot more to do.

Let me just finish by describing how we are going about making sure that we make the right decisions about what to do.

PREPARED STATEMENT

We recently finished a 9-month process with the leukemia, lymphoma, and myeloma community, including researchers, clinicians, patients, and advocacy groups, to create a strategic plan outlining what we need to do, what we need to know, what barriers we need to overcome to create a more definitive and successful research program against these diseases. This is called a PRG, or Progress Review Group. It has been a marvelous partnership among the entire community. We have now received this report, and over the next year will be working with the community to very aggressively implement the many recommendations. There is an enormous amount to be done, but I think there are few areas of cancer where the progress in science has as much possibility for rapid application than in this diverse set of diseases.

So, I appreciate your attention to these diseases and for having this hearing.

[The statement follows:]

PREPARED STATEMENT OF RICHARD KLAUSNER

Good morning. I am Richard Klausner, M.D., Director of the National Cancer Institute. Thank you, Chairman Harkin, Senator Specter, and distinguished Members of the Subcommittee for inviting me to speak with you about research on hematologic cancers.

Despite advances in diagnosis and treatment and improvements in patient survival, hematologic cancers continue to have a significant impact on the lives of Americans. Right now, almost 700,000 Americans are living with leukemia, lymphoma, or myeloma (LLM), and an estimated 100,000 new cases occur each year. Although mortality has declined and 5-year survival rates have increased among adults and children with certain forms of these diseases, an estimated 60,000 Americans will die of them in 2001. For all forms of leukemia, the five-year survival rate is only 46 percent, for non-Hodgkin's lymphoma it is 54.2 percent, and for multiple myeloma it is only 28 percent. Despite the significant decline in the death rate for children with leukemia, this disease still causes more deaths in children in the United States than any other disease. Furthermore, the death rates for non-Hodgkin's lymphoma and multiple myeloma are increasing at a time when death rates for other cancers are dropping. Since the 1970's, incidence rates for non-Hodgkin's lymphoma have nearly doubled, although during the 1990's the rate of increase appeared to slow. Hematologic cancers strike individuals of all ages, from children to the elderly; men and women; and all races.

WHAT ARE LEUKEMIA, LYMPHOMA, AND MULTIPLE MYELOMA?

To understand these diseases, we must first understand the normal development of the cells they affect. Hematopoiesis is the process by which blood cells form and mature. All the different types of blood cells arise in the bone marrow from a common pluripotent hematopoietic stem cell, and undergo a series of developmental steps to differentiate into mature cells and assume specific roles in the body. New, immature blood cells may stay in the marrow to mature or may travel to other parts of the body to mature. Normally, blood cells are produced in an orderly, controlled way, as the body needs them. Some circulate throughout our bodies via blood vessels and lymph vessels. Some reside in the lymphatic tissues that are primarily concentrated in lymph nodes, thymus, spleen, and in most of our major organ systems.

Leukemia, lymphoma, and multiple myeloma are all cancers of the blood-forming organs, or hematopoietic neoplasms. They arise due to errors in the genetic informa-

tion of an immature blood cell. As a consequence of these errors, the cell's development is arrested so that it does not mature further, but is instead replicated over and over again, resulting in a proliferation of abnormal blood cells. Nearly every stage of the hematopoietic process can give rise to a distinct type of cancer.

Historically, scientists and physicians have classified these diseases by their locations in the body, the appearance of affected cells under the microscope, and the natural progression of the diseases. In leukemia, the cancerous cells are discovered circulating in the blood and bone marrow, while in lymphoma, the cells tend to aggregate and form masses, or tumors, in lymphatic tissues. Myeloma is a tumor of the bone marrow, and involves a specific subset of white blood cells that produce a distinctive protein.

Leukemia can arise in either of two main groups of white blood cell types—lymphocytes or myelocytes. Either type of leukemia can be acute, a rapidly progressing form of the disease in which the affected cells are very immature and unable to serve their proper purpose, or chronic, which progresses more slowly and is distinguished by cells that are relatively well differentiated but still function poorly. Lymphoma involves lymphocytes and can also be subclassified. Non-Hodgkin's lymphoma (NHL) is the more prevalent form of the disease. Among non-Hodgkin's lymphomas, indolent disease progresses slowly and exhibits well-differentiated lymphocytes, while the more aggressive forms are characterized by lymphocytes with far less differentiation. Hodgkin's disease, which is less common than NHL and has different clinical and epidemiological features, has historically been distinguished from NHL by the presence of distinctive cells called Reed-Sternberg cells.

Leukemias, lymphomas, and myelomas share some common features, but there are major differences among them—and there are similarities and differences within each disease group. These cancers actually represent a large number of diseases that vary significantly in their causes, molecular profiles, and natural progression. In the past decade we have a experienced a revolution in the field of molecular biology that has brought new tools that are helping us refine cancer classification in terms of the molecular changes that distinguish a normal cell from a cancerous one, and draw differences between cancerous cells of different types.

This is an area of research rich in scientific promise, and the NCI has issued the Director's Challenge: Toward a Molecular Classification of Tumors, in which investigators are creating comprehensive molecular profiles of tumors using DNA, RNA, or protein-based technologies. These profiles will be used to define more informative, and clinically predictive, molecular classification schemes for human cancers.

MOVING TOWARD A NEW UNDERSTANDING OF LLM

A major NCI initiative, the Cancer Genome Anatomy Project (CGAP), has resulted in the cataloging of tens of thousands of human and mouse genes. The CGAP database is a unique resource that allows scientists to develop tools to perform large-scale genomic analyses to characterize tumors genetically. This genetic characterization can help explain why patients diagnosed with the same cancer differ dramatically in their responses to treatment. For example, a collaboration of scientists (including NCI scientists) genetically analyzed diffuse large B-cell lymphoma, an aggressive cancer that is the most common type of non-Hodgkin's lymphoma. For 40 percent of patients with this diagnosis, standard multi-agent chemotherapy is curative. A compelling clinical problem is to understand why the remaining 60 percent of patients succumb to this disease despite chemotherapy. Reasoning that the varying therapeutic responses of patients with diffuse large B-cell lymphoma are due to undefined molecular differences in their tumors, researchers used DNA microarray technology to define the gene expression profiles of diffuse large B-cell lymphoma samples on a genomic scale. This new technology is capable of measuring the activity of tens of thousands of genes at the same time, thus creating a molecular portrait of the cells being studied.

For this study, the CGAP was used to create a specialized DNA microarray, the Lymphochip, which is enriched in genes that function in normal and malignant lymphocytes. Lymphochip microarray analysis of gene expression in diffuse large B-cell lymphoma samples revealed that this single diagnosis actually combines two distinct diseases that differ in the expression of hundreds of genes. The two types of diffuse large B-cell lymphoma that were discovered each resemble a different type of normal B lymphocyte, suggesting that these cancers have distinct cellular origins. Clinically, patients with these two types of diffuse large B-cell lymphoma had strikingly different responses to chemotherapy. Patients with one lymphoma subtype, termed germinal center B-like diffuse large B-cell lymphoma, had a favorable prognosis: 75 percent of these patients were cured by chemotherapy. Patients with the other lymphoma subtype, termed activated B-like diffuse large B-cell lymphoma,

had a poor response to chemotherapy with less than one quarter of these patients achieving a long-term remission. This study provides a clear demonstration that genomic-scale gene expression analysis can define clinically important subtypes of human cancer.

This powerful new technology is now being used to study many different types of cancers, including leukemia and multiple myeloma, in an attempt to identify disease subgroups. For example, a new project, "Molecular Taxonomy of Pediatric and Adult Acute Leukemia," will attempt to correlate the expression pattern of over 30,000 genes with treatment outcome and with cytogenetic abnormalities for both acute lymphocytic leukemia and acute myeloid leukemia. In the future, such gene expression profiling of cancer cells will be used to guide patients towards therapies that are tailored for their particular diseases.

CAUSES, RISK FACTORS, AND EPIDEMIOLOGY OF LLM

Our understanding of the causes of these diseases is extremely limited, perhaps in part due to extreme heterogeneity of the diseases and the inadequacy of the traditional classification schemes to adequately address this heterogeneity. As our knowledge base about molecular subtypes grows, we hope that we will be better able to understand the relationships between causative factors and the development of LLM.

Leukemia

The leukemias are very heterogeneous, with patterns of occurrence differing by age, sex, and racial and ethnic group. For example, highest incidence of acute lymphoblastic leukemia (ALL) is in children, ages 2–4, while chronic lymphocytic leukemia (CLL) is rare before age 30, and has the highest incidence among the elderly. Chronic myeloid leukemia (CML) has a higher incidence among African-Americans than Caucasians, while the incidence of CLL is highest among Caucasians and extremely rare in Asians.

The causes of leukemia in children and adults are largely unknown, but increased or decreased risks for developing leukemia have been associated with several factors. In an ongoing, collaborative follow-up study with Japanese investigators, NCI scientists have found strong evidence of radiation-induced risks for the acute leukemias and CML among Japanese atomic bomb survivors. NCI investigators and others have shown that radiotherapy and chemotherapy for a wide variety of diseases have been linked with moderately increased risks of acute myeloid leukemia (AML), although the benefits of treatment far outweigh the risks.

Occupational exposures to ionizing radiation and certain chemicals such as benzene have also been linked with increased risk of acute leukemia. NCI is conducting an epidemiologic study of workers in China exposed to benzene at levels lower than previously studied, to characterize leukemia rates and to determine mechanisms of action and factors affecting carcinogenicity of benzene. In addition, cigarette smoking has been associated with modest increases in acute leukemia but the evidence is not yet conclusive.

The first known human retrovirus, T-lymphotropic virus type 1 (HTLV–1), discovered at NCI in 1981, is the primary cause of adult leukemia and lymphoma arising from lymphocytes known as T cells. Certain genetic conditions can increase the risk for acute leukemia, including Li-Fraumeni syndrome, Down's syndrome, Bloom's syndrome and several other rare conditions.

Lymphoma

NCI investigators have recently reported on investigations of lymphoma incidence trends. Over the last ten years, researchers have studied the histologic types of lymphoma that are on the rise; illnesses, including other cancers, associated with lymphoma; occupational groups that may be at increased risks; and the role of genetic susceptibility. Recent research has identified several possible candidates for increasing risk including pesticides, organochlorine compounds, solvents, drinking water nitrates, and hair dyes. We are now evaluating whether these common exposures are contributing to the rise in NHL among some populations and investigating other hypothesized risk factors such as infectious agents, medical conditions, medical treatments, and genetic factors.

There has been considerable research on the association between infectious agents and cancer. Helicobacter pylori is a bacterium associated with a particular rare type of lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma that arises in the stomach. Both Hodgkin's disease and non-Hodgkin's lymphoma, particularly some of the more aggressive forms, occur with increased frequency among adults and children infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. In HIV-infected patients, about one-half of all lymphomas involving

a type of lymphocytes called B cells are associated with the Epstein-Barr virus, including virtually all primary central nervous system lymphomas in patients with AIDS. A new Program Announcement, in collaboration with National Institute for Dental and Craniofacial Research, is being issued to stimulate research on viruses associated with the development of lymphomas among persons who are infected with HIV. The AIDS-Cancer Cohort is studying men infected with HIV to examine interactions with various environmental exposures that may contribute to the excess risk of lymphoma. Information from this project may be of value beyond the setting of HIV, as it may yield more fundamental biologic understanding of the interplay of viruses and chemicals in the development of lymphoma. A rare type of lymphoma, called Primary Effusion Lymphoma, which arises in the lining of the lung, heart or abdomen, is tightly linked to, and probably caused by, the Kaposi's sarcoma herpes virus (KSHV). People who have both HIV and KSHV are at particularly high risk. Because viruses similar to KSHV are known to cause lymphoma in animals, efforts are in progress to identify new, lymphoma-related viruses in people.

NCI scientists are conducting very large epidemiologic studies addressing the relationship between the environment and lymphoma development. In a population-based case-control study of non-Hodgkin's lymphoma, NCI investigators, collaborating with the Centers for Disease Control and Prevention (CDC), assessed exposures to pesticides, solvents, and other factors using computer-assisted personal interviews, residential carpet dust samples, drinking water samples, and blood samples. Analysis continues, as investigators extract DNA from blood or saliva samples to assess the interaction between genetic variations and environmental risk factors.

The Agricultural Health Study (AHS) is following 90,000 healthy farmers and their family members in Iowa and North Carolina in an effort to measure their risks of developing lymphoma and leukemia. NCI and National Institute of Environmental Health Sciences launched the AHS in 1993 after previous NCI research implicated occupational exposures to pesticides in the development of lymphoma. The study assesses the risks of other cancers and diseases, as well.

A new initiative called Interlymph, coordinated by NCI and involving investigators in Europe and Australia, features a pooled and simultaneous analysis of thirteen case-control epidemiologic studies of non-Hodgkin's lymphoma. The international consortium of collaborators will examine pathology, infectious agents, family history data, genetic factors, and methodologies needed to accurately assess possible links with the development of lymphoma.

Multiple Myeloma

The median age for diagnosis of multiple myeloma is 71 years of age. The incidence of multiple myeloma is much higher in blacks than whites, and is higher among males. Similar to incidence rates, the death rates are higher among males than females and higher among blacks than whites. This is one of the few cancer sites in which the survival rate is higher for blacks than for whites. The causes of multiple myeloma and the reasons for the racial disparity in incidence are unclear.

Some studies have suggested the role of ionizing radiation, certain organic solvents and chemicals, as well as employment in farming and agricultural occupations. In recent studies, genetic factors, low socioeconomic status (SES), and obesity have been implicated. Recent attention has also focused on viruses and other infectious agents, but their role in the etiology of myeloma remains unclear. There is growing evidence that certain cytokines and chromosomal abnormalities may be involved in the pathogenesis of multiple myeloma. These laboratory-based genetic measures need to be incorporated into future epidemiologic studies to better understand the complex relationships between genetic and environmental factors in the development of this disease.

In a recent study, NCI investigators found that low SES, whether measured by occupation-based SES, income, or education, may account for about half of the excess incidence observed among blacks. Low SES may be a surrogate for a set of negative environmental characteristics, such as poor housing, dangerous jobs, lack of access to medical care, poor nutrition, and exposure to infectious agents, all of which may have a role in this disease.

The rarity of this cancer makes it difficult to adequately investigate in a single study, so that collaborative efforts involving a variety of hematopoietic malignancies are being pursued.

NEW STRATEGIES FOR TREATMENT OF LLM

Therapeutic research in the treatment of patients with hematologic malignancies has made enormous progress over the past 50 years, and the NCI has shepherded this important work. Many years ago, NCI established the National Service Center to enable basic scientists to design and test chemical agents for evidence of anti-

tumor activity. In addition to pioneering cancer drug screening, the NCI funded an entire preclinical drug discovery and development program. The NCI has continuously supported investigators to pursue all phases of clinical evaluation of products emanating from their own discovery and developmental efforts, and interacts with the pharmaceutical industry and academic institutions to explore their novel agents.

In the last decade, there has been an enormous investment in defining molecularly targeted agents in cancer chemotherapy. Recently we have seen some inspiring success stories, all of them direct results of this new approach. The first evidence of a consistent gene mutation associated with a particular cancer was provided about 40 years ago by the recognition of the Philadelphia chromosome, an abnormally small chromosome 22, in chronic myeloid leukemia (CML). Some years later, researchers noted that while chromosome 22 was shortened, chromosome 9 was lengthened in CML patients, which suggested that the pieces of each chromosome were exchanged, or translocated. This observation was followed by the identification of a unique fusion gene, called *bcr-abl*, resulting from the translocation, and the eventual development 5 years ago of one of the first oncogene-targeted drugs, STI571 or Gleevec. This compound, which was recently approved by the United States Food and Drug Administration (FDA), is directed at the *bcr-abl* gene product, which is expressed in about 95 percent of CML patients, and in some patients with other types of cancers. Gleevec has shown remarkable promise in the treatment of chronic-phase CML, and NCI is partnering with Novartis, the drug manufacturer, to facilitate a profusion of clinical trials evaluating Gleevec in other cancers, including Philadelphia chromosome-positive ALL in adults and children. Additional trials are assessing the potential benefits of combining Gleevec with other chemotherapeutic agents. Molecular analyses of other types of leukemia have now produced the identification of more than 100 additional oncogene targets that may be accessible to similar drug development strategies.

Monoclonal antibodies are showing great promise in the treatment LLM. Among them, Rituximab, which was originally approved by the FDA in 1997 for the treatment of non-Hodgkin's lymphoma (NHL), is an antibody directed at a cell surface antigen expressed on B lymphocytes and has been shown to be effective against many types of B cell malignancies. Currently, for both children and adults, rituximab is under study in combination with other therapies, including other monoclonal antibodies, attempting to attack multiple targets on a single cell type.

In addition, NCI-sponsored studies are evaluating several new antibodies. Generally, leukemias, lymphomas, and multiple myelomas are derived from cells of the immune system and therefore frequently express antigens that are present on normal immune cells such as B-cells or T-cells. Since these proteins are not present on other human cells and are not present on the stem cells that give rise to normal B-cells and the T-cells, the antigens are excellent targets for cancer therapy. NCI researchers have devised a cancer treatment strategy that kills cells containing B-cell or T-cell specific antigens. When this occurs the normal cells are regenerated, but the cancer cells are not. One strategy is to fuse the portions of antibodies that bind to CD22 (a B-cell antigen) or CD25 (a T-cell antigen) to a potent bacterial toxin termed Pseudomonas exotoxin A. The genetically modified toxin then specifically binds to and kills cells expressing CD22 or CD25. Since many lymphomas and leukemias express CD22 or CD25, these tumor cells are killed.

A promising ongoing NCI study is using this approach to combat B-cell malignancies. The antigen CD22 is expressed on about 70 percent of lymphomas and leukemias. A recombinant immunotoxin termed BL22 has been designed and produced to kill tumor cells expressing CD22, and patients with hairy cell leukemia, chronic lymphocytic leukemia (CLL), and some lymphomas have been treated in a Phase I trial. Remarkable anti-tumor activity has been observed in patients with hairy cell leukemia. Several patients with CLL have responded as well. Enrollment into this trial is continuing, and once the maximum tolerated dose is established, Phase II trials in hairy cell leukemia, CLL, and lymphomas (in a post-transplant setting) will be opened for enrollment.

Other antibodies under investigation are coupled to other potent anti-tumor substances, like radioactive molecules or anti-tumor antibiotics, and have the potential advantage of being able to deliver this tumor killing substance directly to the tumor site, where they attack antigen-positive tumor cells that other therapeutic agents might not penetrate well.

Anti-cancer vaccines are a high priority research area for NCI. Unlike conventional vaccines, which are used to prevent illness, the anti-cancer vaccines represent a therapeutic approach, which seeks to strengthen the body's natural defenses against diseases, such as cancer, that have already developed. Vaccine therapy for lymphomas has shown considerable promise. Results of a recently completed lymphoma vaccine study conducted by NCI researchers have shown that there is a

clear anti-tumor effect in a small group of patients who were vaccinated over the course of five years. On the basis of these promising results, NCI has launched a large-scale, multi-institutional, randomized, phase III clinical trial, to definitively test the experimental vaccine, which is custom-made from patients' own tumors.

Immunotherapeutic approaches for treatment of multiple myeloma are also being evaluated. Investigators are examining the potential for immunization strategies in which a normal donor is vaccinated with the myeloma protein. The normal donor forms antibodies, called idiotype antibodies, and these are used to treat the patient. Preclinical studies of idiotype immunization demonstrate that this approach can induce an immune response that prevents tumor relapse or progression in myeloma models. Additional studies are determining the feasibility of inducing an active immune response against myeloma-specific antigens, such as MUC–1 and DF3.

The NCI is involved in the development of a large number of new therapeutic agents with a wide array of unique mechanisms of action. We now know that cancer arises from the disruption of fundamental cell processes. Basic research findings have identified a plethora of potential therapeutic targets for further exploitation. There is an ever-lengthening list of promising agents that affect cell cycle regulation, gene expression, apoptosis (programmed cell death), and other cell functions, currently undergoing or awaiting investigation in clinical trials.

A striking example of the benefit of this kind of molecularly targeted therapy is all-trans retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia (APL). ATRA works essentially by reversing the effects of a specific chromosomal translocation that disables both differentiation and apoptotic processes in affected cells. The introduction of this agent has increased the cure rate for APL from 40 percent to over 70 percent in just 10 years. Some patients who have been treated successfully with ATRA experience relapse, and recently, arsenicals, a group of rediscovered compounds that induce apoptosis via a different, more broadly applicable mechanism, have shown great utility as a second line of defense against APL. Arsenic trioxide is now being evaluated for use in a variety of lymphoid malignancies, as well as other cancers, and for use in childhood APL, and also for use as a first line treatment.

Finding effective treatments for multiple myeloma has proven extremely challenging for cancer researchers. Recently, the success of thalidomide in treating MM patients has been very encouraging. Thalidomide effectively arrests tumor growth by stimulating anti-tumor immune response, interfering with communication between tumor cells and the surrounding tissue, and inhibiting the growth of new blood vessels (angiogenesis) near the tumor. Thalidomide's anti-angiogenic activity, was first recognized as the feature that caused birth defects in the children of women who took thalidomide in the 1950's and 1960's. Astute researchers theorized that the same feature could prove useful in restricting the blood supply to tumors. NCI-sponsored investigators recently report a 30 percent response rate for MM patients receiving thalidomide on a clinical trial. New trials are seeking to optimize the role of this agent, and some other antiangiogenic agents are being evaluated, as well. Because anti-angiogenic drugs have the potential to cause defects in a developing fetus, pregnant woman are excluded from participating in clinical research on these drugs.

Bone marrow transplantation and peripheral blood stem cell transplantation techniques continue to be tested in clinical trials for certain LLM patients. Sometimes cancers become resistant to treatment with radiation therapy or chemotherapy. Very high doses of chemotherapy may then be used to treat the cancer. Because the high doses of chemotherapy can destroy the bone marrow, marrow is taken from the bones before treatment. The marrow is then frozen, and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer. The marrow is then thawed and given back to the patient to replace the marrow that was destroyed. This type of transplant is called an autologous transplant. If the marrow is taken from another person, the transplant is called an allogeneic transplant. Another type of autologous transplant is called a peripheral blood stem cell transplant. The patient's circulating stem cells are collected, treated with drugs to kill any cancer cells, then frozen until they are returned to the patient. This procedure may be done alone or with an autologous bone marrow transplant.

The role of stem cell transplantation in caring for patients with LLM varies with tumor type. Autologous stem cell transplantation clearly benefits patients in a chemotherapy-sensitive relapse of their disease, but its role as initial treatment is undefined. A national trial is comparing the efficacy of initial transplantation with transplantation at the time of first relapse. Other studies are evaluating the role of biological therapies such as interleukin-2, and immune response stimulator, and rituximab for their effectiveness in enhancing the benefit of transplantation.

Many patients do not benefit from stem cell transplantation, and major efforts are directed at identifying the reasons and to develop methods to improve on these results. Some investigators are developing methods to harness patients' own immune responses. Alternatively, other researchers are using a technique called donor leukocyte infusion (DLI) that introduces T cells capable of generating a graft-versus-tumor effect (in which the donor cells attack the patient's cancerous cells). However, they are also capable of generating a potent graft-versus-host disease (GVHD, in which the donor cells attack the healthy tissues of the patient) that could be fatal to the patient. Studies of the array of T cells that are present post DLI are being conducted to better understand which T cell populations are necessary to achieve the desired result while minimizing GVHD.

Allogeneic bone marrow transplant may cure patients who do not respond to standard chemotherapy, but the mortality of this procedure in patients with LLM has been very high. Moreover, age restrictions limit the number of patients who might be eligible for this procedure. There has now been an expanded information base on the use, for non-Hodgkin's lymphoma, of non-myeloablative transplants (in which the bone marrow is not completely destroyed) with DLI. Recently, investigators have described their experience with patients over the age of 55 years. GVHD occurred less frequently than expected and many patients were able to go through the procedure without requiring hospitalization. As a consequence, the notion that more intensive treatment is better is being challenged, and the role of the immune system in cancer progression is being better delineated.

The NCI sponsors the International Bone Marrow Transplant Registry, which is the world's largest body of data on outcomes following transplantation for LLM and other cancers. Data are provided from more than 400 centers and there are now data for more than 65,000 transplants worldwide. The information collected is used for determining transplant regimens for specific clinical situations, identifying prognostic factors, comparing transplant regimens, comparing transplant with non-transplant approaches, evaluating cost and cost-effectiveness, planning clinical trials, and developing approaches to evaluate outcomes.

Clinical trials for LLM treatment have demonstrated remarkable success and are a vital component of the NCI's research program. Currently, our clinical trials database contains descriptions of 177 NCI-sponsored leukemia treatment trials, 170 for lymphoma, and 67 for multiple myeloma. Our clinical trials program is the place where promising new strategies discovered at the laboratory bench are applied to real human problems at the bedside. Clinical trials offer cancer patients access to state-of-the-art care, and provide us the opportunity to learn something from every patient that may help someone else. Our rapid pace of discovery in the basic biology of cancer is refining our knowledge of how to intervene in cancer development, and clinical trials are the crucial final step in bringing these discoveries to people who are battling cancer.

CONCLUSION

Progress in our understanding of cancer and our ability to detect and treat it have led to a real and continuing decline in the cancer incidence and death rates. However, our excitement over important scientific progress and the very real human gains that result is tempered by the knowledge that far too many Americans continue to suffer and die from cancer each day. Moreover, all groups of people are not benefiting equally from our advances against cancer. NCI is embracing the challenge of understanding the causes of health disparities in cancer and developing effective interventions to reduce them. Plans call for increasing fundamental research into the social causes of health disparities, the psychosocial factors that mediate them, and the biologic pathways that can explain their impact. In addition, we will expand our cancer control intervention and population research on disparities, better define and monitor cancer-related health disparities, and strengthen training and education in this research area. Effective communication empowers people to make informed cancer-related decisions and to engage in behaviors that will improve their health. Few other initiatives have the potential to simultaneously improve health outcomes, decrease health care costs, and enhance community satisfaction. Our intent is to learn how to help people distinguish important from insignificant health risks and deal with contradictory or inaccurate health messages so they can make informed choices.

Too many Americans, for a host of reasons, lack access to high quality, cutting-edge cancer treatment and care. NCI is launching research to improve the quality of cancer care by strengthening the information base for cancer care decision making. Researchers seek to better understand what constitutes quality cancer care, with an emphasis on the patient's perspective; identify geographic, racial/ethnic, and

other disparities in who receives quality care; and strengthen the scientific basis for selecting appropriate interventions. Our goal is to enhance the state of the science for defining, monitoring, and improving the quality of cancer care and inform Federal decision making on cancer care delivery, coverage, and regulation.

We have learned the value of including as broad a constituency as possible in our review, advisory, and planning activities, and we have forged new relationships with patients, practitioners, scientists in different fields of research and medicine, other government agencies, private sector companies, innovators in technology, and many other partners where such alliances were rare or non-existent only a few years ago. Illustrating our commitment to this philosophy as we seek to accelerate progress against LLM, the NCI convened a Progress Review Group (PRG) last year to conduct an intensive review of our research portfolio in LLM. This initiative, one of a highly beneficial series of PRG's fitting within NCI's new disease-specific planning framework, featured expert panels who provided a comprehensive view of the state of our current knowledge, and you will see that many of our research priorities will reflect the recommendations the PRG described in their report, issued last month, and available on our website at: http://osp.nci.nih.gov/prg assess/prg/llmprg/ llm rpt.htm.

We have a special interest in enlisting the help of cancer survivors. The NCI created the Consumer Advocates in Research and Related Activities (CARRA) program to encourage people affected by cancer to provide their viewpoint and ideas directly to NCI staff so that the NCI can incorporate this perspective into our programs and activities. Our goal is to recruit 150 consumer advocates (cancer survivors, family members, or those who are involved in cancer-related activities like support groups, cancer hot lines, or advocacy groups) to become members of CARRA and represent many different cancer types, age groups, and ethnic groups from across the Nation. In addition to participating in NCI activities, CARRA members will represent the opinions of their groups and play critical roles as two-way information links between their own communities and constituencies and the NCI.

NCI has been entrusted with guiding our Nation's commitment to a complete understanding of cancer: from understanding how a normal cell becomes cancerous to understanding why some people get cancer and others do not; and across the continuum through detection, diagnosis, treatment, survivorship, and ultimately prevention. NCI's mission is broad and our approach is necessarily ambitious, because, while our primary role and our expertise is research, our interest is people: our families, friends, neighbors, and colleagues—and yours. Our goal is to eradicate cancer and save the lives of those who would otherwise be lost to us.

Thank you, Mr. Chairman, for giving me this opportunity to share with you our progress against hematologic cancers. I will be pleased to answer any questions you may have.

STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER [presiding]. Well, thank you very much, Dr. Klausner for your lucid testimony, as usual.

First, I want to acknowledge the generous comments made by Senator Harkin who noted his chairmanship of this subcommittee from 1989 through 1994, and mine from 1995 through a few days ago. We have worked really for a common purpose. I learned a long time ago if you want to get something done in Washington, you have to cross party lines, and so far as this subcommittee's activities, I think it makes little, if any, difference as to who has the gavel.

We have pursued funding for NIH in a very vigorous way, as everyone knows. We have added more than $8 billion in increases for the NIH and we are on a path to double funding over 5 years. This year we have targeted and increase of $3.4 billion. Each time we have gone to the Budget Committee for more money, we have gotten congratulations but no additional cash. We have had to establish priorities within the subcommittee.

We have had a whole series of hearings on a variety of special ailments, muscular dystrophy, amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, so many, many ailments. We responded to a

special request by our colleague, Senator Kay Bailey Hutchison, whose brother suffers from myeloma, and also made the subcommittee aware former Congresswoman, Vice Presidential candidate Geraldine Ferraro has this ailment.

We have held these hearings because of an effort to create public awareness as to the fact that some serious malady can affect anyone of you or your family. We try to get public support for research for NIH and, beyond that, research for implementing the NIH funds. For example, on stem cell research, you testified in this room just a few weeks ago, Dr. Klausner, as to the impact stem cells could have on cancer. We had a private follow-up conversation.

I regret that we do not have a bigger room. We have a line which goes for several blocks outside, which signifies how much public interest there is in this subject and all taxpayers should have the opportunity to hear the testimony.

Senator HUTCHISON. Mr. Chairman, could I just make a suggestion on that point? There are so many people outside, that I wondered if after about 30 minutes, some of you might rotate out and let them come in, just on a voluntary basis so that everyone has a chance to see some part of the hearing.

Senator SPECTER. I think that is a good idea, Senator Hutchison.

You folks in the rear can move up to the sides, and anybody who would like to be a Senator for a hearing can take some of these seats. You may have to leave if some more of our colleagues come. But come on up. Come on up to the side so that we can have the maximum number of people come in at the present time.

I want to make one additional comment this morning that I had not intended to make, but there is a front-page story in the Washington Post today which I find very disquieting, and that is about administration testimony given yesterday to a subcommittee of the House of Representatives on the issue of stem cells.

This is generally known. These stem cells are extracted from embryos which are going to be thrown away. At the present time, there is a ban on any Federal funding being used to extract stem cells from embryos. But there is currently a ruling by the general counsel for the Department of Health and Human Services that once the embryos are removed, that Federal funds can be used for stem cell research.

The administration, according to this morning's press—and I am going to have to read the transcript and get the statements—is making the suggestion that that is subject to change by the President. I do not know about that. If you have a lawyer's opinion given by the general counsel for the Department of Health and Human Services that it is appropriate to fund research on stem cells, once extracted, it seems to me that is that, especially in the context where that ruling was made some time ago, and the Congress has not changed it. There is a presumption which attaches to a ruling of that sort where Congress has not made a change. If Congress disagrees with that, Congress can make a change in it.

Senator Harkin and I and others have been working very hard on the issue to get support, even to rescind the ban on use of Federal funds for extracting stem cells from embryos. One of our colleagues, Senator Gordon Smith, a very strong pro-life Republican—

and many who favor use of Federal funds to extract stem cells on the research are pro-life Republicans. But Senator Gordon made a very valid point, that it is different if you have an embryo in a dish as opposed to having an embryo in a womb. If you have an embryo in a woman's womb, there is movement toward life. If you have an embryo in a dish and so many of them are destroyed, there is just no real reason not to use those embryos to save lives since they are going to be discarded.

Now, it may well be that the scope of the administration's position is narrow enough so that it will not impact on either of the two questions: one, use of Federal funds on the stem cells once taken from the embryos; or on the second question, use of Federal funds to remove stem cells from embryos.

We have been talking among Senators and it may well be that we have more than 70 votes in the U.S. Senate to remove the ban on using Federal funds for extracting stem cells from embryos. Senator Lott had agreed to bring the bill up which Senator Harkin and I and many others have introduced as a freestanding bill, and I have talked with the new Democratic leadership and bringing the bill up may be right around the corner. In the meantime, we are trying to deal with the administration to see to it they will make the ruling to allow Federal researches to extract their own stem cells.

After I yield to Senator Hutchison, Dr. Klausner, I am going to come back to you on the issue of stem cells as an assist on the kinds of research and treatment you are describing here today.

Senator Hutchison, we thank you for suggesting this hearing and give you the floor.

STATEMENT OF SENATOR KAY BAILEY HUTCHISON

Senator HUTCHISON. Thank you, Mr. Chairman and ranking member. When Senator Specter was the chairman of this subcommittee, I did talk to him about having this hearing. When Senator Harkin then became chairman, he agreed to continue. I want to thank you so much for leading the way and thank Senator Harkin for continuing his interest because this is such an important issue, one which I think has not gotten as much of the research and the focus as perhaps now we will be able to do.

When I first started looking into the Federal commitment to the deadly blood cancers, leukemia, lymphoma, and multiple myeloma, I was really amazed to know that 11 percent of all cancer deaths come from these blood diseases, but only 5 percent of the research funding from the National Cancer Institute is going to find the cure to these cancers.

I talked to Dr. Klausner about that personally 2 years ago, and he could not have been more responsive. I appreciate so much your willingness to listen and to act on the concerns that we had. You set up the Progress Review Group, which now is able to review and advise the National Cancer Institute, and I really appreciate that. I think that is a major step forward.

Nevertheless, this is now, I think, an area where we are seeing new innovations, and, because of my personal interest in it, I know that some of the innovations, such as thalidomide, are coming for-

ward. There are others. So, now I think there is something to really invest in.

Because of that, I want to say that I am introducing a bill today with my colleague, Senator Barbara Mikulski, that will direct the National Cancer Institute to establish a program for research of lymphoma, multiple myeloma, and leukemia. It will authorize $250 million for that purpose and it will also add $25 million for education efforts because, as you know, early detection can save lives in any kind of cancer. We have seen the incredible results in breast cancer of early detection through education and awareness. I want to do that for the blood cancers as well.

Along that line, more than anything that I could ever have done, there are people who have been willing to step up to the plate and say, wait a minute. I have now come in contact with this disease. I now see how neglected it has been in the area of research. I think what Geraldine Ferraro is doing for the future of the research capabilities is beyond any of our expectations, and I want to thank her for coming forward and saying let us do something about this.

It was Geraldine Ferraro who called me several months ago and said she wanted to make sure that we do something that will push this issue to the forefront, which resulted in this hearing. I went to Senator Specter and I told him of her willingness to come forward and be helpful in the education and awareness efforts. Thank you. What you are doing is going to have huge benefits.

I want to also just thank one other person, Kathy Giusti, because it was Kathy who never gave up. She is the head of the Multiple Myeloma Research Foundation. I call her a human hurricane. It is true. She has done so much to make this happen. She came forward. It takes time to get these things done, but I think the culmination of your efforts is happening this week. I thank you for that bravery.

Dr. Ken Anderson, Geraldine Ferraro's physician, is doing so much and is so committed from his heart to the research.

I also want to thank Dr. Kantarjian, who is a renowned physician and researcher in the area of leukemia at the Nation's number one cancer center, M.D. Anderson. Dr. Kantarjian actually cut short his much deserved vacation to testify today, and I thank him for his efforts.

Last but not least, I want to say that I would not have really been aware of this had my brother not been willing to step forward. I went through a bone marrow transplant. We will be there for you. Thank you.

Senator SPECTER. Thank you very much.

Senator Murray, would you care to make an opening statement?

STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Mr. Chairman, let me thank you and Senator Harkin and Senator Hutchison for your tremendous passion on this. I think it is shared by clearly all the people in this room. This is really an impressive hearing to have so many people here today. I know how difficult it has been to schedule this hearing with all that is going on on the floor in the Patients' Bill of Rights and all of the changes in the Senate, but clearly this is important.

I have a number of constituents who have come here from Washington State. I had to spend a few minutes in the hall with them because they cannot get in the room. They have traveled 3,000 miles to be here. So, I hope at some point they do get to get in the room and hear part of this hearing.

But I just want to thank everybody who has come because I think your presence alone shows the impact on this country.

I too want to thank Geraldine Ferraro for her courage. I think in the last few days the awareness of the American public of this impact on people and their lives and the awareness that they have of the importance of research has just grown unbelievably large, and that is because of your courage. I just want to tell you how much I appreciate your doing this. We are in this fight with you, and thank you for being here today.

Mr. Chairman, I know we have a number of panels who are coming before us. I look forward to offering our questions as they come through. Thank you very much.

Senator SPECTER. Thank you very much, Senator Murray.

We still do have some more room here. We have some more chairs. If anybody in the hall wants to come up and sit on the floor, it is not the most gentile, but you would be a part of the hearing. Let us make that offer to those who are outside. We have a very large group of people outside who we regret are not accommodated here.

Dr. Klausner, Senator Harkin, the chairman, has yielded to me for the first round of questions. We will have 5-minute rounds. Let me say we are going to have to move right along. We have a lot of witnesses, and we have a markup on the supplemental appropriation bill at 11:30 this morning. So, everybody on this panel will be involved in that.

Dr. Klausner, I want to start with a statement which you made which summarizes the issue of stem cells on this particular ailment. The subcommittee had asked you for your views on stem cells, and you wrote the following. "Probably the most dramatic recent advancement which arose from stem cell research is the development of the drug Gleevec for the treatment of chronic myelogenous leukemia, CML. The development of this drug came as a result of the careful step-wise studies of CML cells compared to normal cells. This drug is unique in that it results in remissions in nearly 100 percent of patients who take it as initial therapy, has minimal side effects, and is a pill. Furthermore, there are data that this drug may have even broader application."

I want to move to an issue raised in yesterday's House hearing which talks about cloning of embryos. Certainly we can use existing embryos that are going to be discarded without having the cloning of embryos. To the extent that there is a consensus against cloning, we do not have to use that as a reason for not using stem cell research.

The question I have for you is that apparently there was some testimony from biomedical researchers, as the news report says, who believe that studies on stem cells from 5-day-old cloned human embryos offers the best chance of developing promising new therapies for a variety of debilitating diseases. My question to you, is

there anything to that? Are the cloned embryos which produce stem cells superior to the discarded embryos?

Dr. KLAUSNER. There is no scientific data that I am aware of that compares cloned human embryos to the embryonic stem cells that can be removed from and then grown as permanent lines from early embryos.

Senator SPECTER. Among the varieties of stem cells which are possible, adult stem cells, fetal tissue, the whole range, I think it would be good for you to put on the record the superiority of embryonic stem cells in scientific research such as you have been referring to.

Dr. KLAUSNER. Yes. We have that information from the mouse where we have been able to compare adult stem cells to embryonic stem cells. In the mouse it is very clear that in embryonic stem cells, the capacity to grow, the persistence, the reliability, the lack of genetic problems, the question of genetic mistakes or genetic damage in cells, and the true pluripotentiality, the ability of those cells to give rise to many, many different types of cell specificities or lineages are superior characteristics to adult stem cells.

Senator SPECTER. I would like to have your verification and comment on other statements made by you that in cancer treatment you destroy cells. It is a destructive process to try to eliminate cancer, and then the stem cells are critically important as they come into the human body to replace the cells which have been destroyed. Would you amplify on that please?

Dr. KLAUSNER. Yes. We have talked a lot about the promises of stem cells for a variety of different diseases. Most of these diseases are degenerative diseases where you need to replace cells, and so it is regenerative medicine, this hoped-for field, that people put most of their hopes on for direct impact of stem cells.

And as I have said to you, cancer is sort of the opposite. It is not a degenerative disease; it is the opposite, a disease where cells proliferate. But in that process normal tissues are damaged, injured, or even killed both from the disease and from the current therapy. So, the indirect place where stem cell and regenerative medicine is hoped for to be helpful, or useful, in cancer would be to replace damaged tissue.

Senator SPECTER. One final question. The yellow light just turned to red, but let me ask just one final question. And that is, from your letter, you make the comment, probably the most dramatic advancement is the drug Gleevec in the treatment of CML. A two-part question. Absent the stem cells, could you have had this dramatic advance and what are the prospects for stem cells to be equally as effective on other forms of cancer?

Dr. KLAUSNER. In the letter, I actually was referring to hematopoietic stem cells, which can be adult stem cells. Studying the derivation of the specialization of blood cells from blood forming stem cells, which are adult stem cells and not embryonic stem cells, allowed the research to go on to understand the molecular changes that happen in CML, chronic myelogenous leukemia. So, this was a general discussion of stem cells. In that particular case, it was not embryonic stem cell research, but rather adult stem cell research.

Senator SPECTER. Well, answer the second part. How badly would you be disadvantaged if you could not use embryonic stem cells in the work which you are pursuing with these very large grants we have gotten for you?

Dr. KLAUSNER. I think the reality is as a scientist, if we cannot do experiments to compare embryonic stem cells to non-embryonic or adult stem cells, we cannot answer the question about what advantages they might have and what we may be missing. As I said, our best experience is from the mouse where the differences are quite clear and the advantages of embryonic stem cells for scientific research are clear.

Senator SPECTER. Thank you very much.

Senator Harkin.

Senator HARKIN [presiding]. Thank you very much, Senator.

Dr. Klausner, I just have one question. I wanted to get into just one small area of this, but it is a very important area, again a report that came out in the Washington Post yesterday. It was the National Cancer Policy Board had a report that said that we are focused so much on finding a cure that we are neglecting research in how to care for people who are dying. The report noted that NCI spent less than 1 percent of its 1999 budget on research and training related to palliative care.

This is an important topic for this hearing because so many people are living with incurable blood cancers. Of course, we do not want to cut down the research on finding the cure, but what can we do to help the people who today are living it deal with the pain and the depression and other symptoms?

I noted that in the press report yesterday, it quoted you as saying that you were very enthusiastic about the report and that you are planning to convene a group to determine how to implement its recommendations. I just wonder if you have anything else that you could tell us about how you plan to proceed on this.

Dr. KLAUSNER. This is a very important report, and it does suggest that all of us need to pay more attention to this. The National Cancer Policy Board, which raised this issue, was actually an idea of mine and I went to the academy to have this set up to provide to the Nation advice about policy issues relevant to cancer that not only affect NCI but actually affect all aspects of decision making in the Federal Government and outside the Federal Government.

This issue of end of life and palliative care is a critical one. We do need to do more research. I am really pleased with the recommendations that the Policy Board has made. Many members of the Policy Board are on our advisory committees. We met last week and we will be looking at ways that we can act on their recommendations to increase research in this area.

Senator HARKIN. I appreciate it. If there is anything this subcommittee can do to be helpful, please let us know.

Dr. KLAUSNER. Thank you.

Senator HARKIN. I would now recognize Senator Hutchison.

Senator HUTCHISON. Thank you, Mr. Chairman, and thank you for holding this hearing, along with Senator Specter. It was a great team effort.

Dr. Klausner, I wanted to ask you specifically what you see going forward with the recommendations of the Progress Review Group

and if you foresee the NCI going in a certain direction in advancing research on the blood cancers now and in the near- to mid-term.

Dr. KLAUSNER. One of the things that I felt about the PRG group, which was a terrific group, and was very satisfying, although you may want to hear from them, was the very nice alignment between their recommendations of where we need to go and the dozens of new programs that we have put in place at NCI to capture the possibilities of new science, new ways of asking questions, to direct them specifically to blood malignancies. I think the PRG recognized that we had set up these structures and we were really set to go, and with these explicit recommendations, we already are working with the members of the PRG within the NCI to figure out what needs to be initiated, what needs to be expanded, and what we will be able to afford to do.

What I really like about the PRG report is the clarity with which it describes how we are going to capture the types of scientific possibilities that I just briefly touched on at the beginning of the hearing in order to make progress. So, we have been mapping all of their recommendations, every single one, against our initiatives, our mechanisms of funding, our funding areas, and then we will be meeting with the PRG group again soon, when we will agree on the mapping and the prioritization of how to go forward.

Senator HUTCHISON. In the last 3 years, it seems that there has been more success at stemming the fatalities, the mortality of the blood cancers. I just wondered if that means that you can do more in research because you have started to build a solid base of research? And where do you think the most promising avenues of research are in the near-term future?

Dr. KLAUSNER. Well, I think there are two issues. One, I think we finally have the tools to correctly classify and diagnose these diseases. I know that sounds very abstract, but if we do not have the right diagnosis for a disease, you cannot actually figure out the right treatment. This is the characteristic of modern medicine. For the first time we believe we have definitive, new tools to correctly classify all these different diseases. Is myeloma one disease? Is it two diseases? Is it five diseases? And it is very hard to find a single treatment for many different diseases.

So, that is the first thing that we have now available to us and if we had enough time, which we do not, we could talk about exactly what we have put in place to challenge the community. In fact, it is a large program around the country called the Director's Challenge where we put out money to definitively molecularly classify all of these diseases for the first time in history.

Then the second part is to finally make use of knowing the difference between each disease. What precisely is wrong in each disease? We need to know the molecular machinery, just like we need to know the machinery that is wrong in a car if we are going to fix it. And finally we need a set of drugs or the immune system to not non-specifically try to kill the cancer, which often does not work, but to very specifically go after what is different between the cancer and the non-cancer, the way antibiotics go after the difference between bacteria and human cells. It is in that arena that we really expect to move forward.

Senator HUTCHISON. Let me just end, because my time is just about up, by asking you a simple question. Are you willing to say that you will be able to put more focus on these blood cancers now that you do have a little more to go on?

Dr. KLAUSNER. Oh, absolutely.

Senator HUTCHISON. Thank you very much.

Senator HARKIN. Thank you, Senator Hutchison.

Senator Murray.

Senator MURRAY. Thank you very much, Mr. Chairman, and thank you for accommodating all the people now. I can see that my constituents have made it into the back of the room and I am delighted.

Senator SPECTER. Senator Murray, there is no one in the hall. We have a lot of people sitting. We brought the last group in to sit on the floor up front.

Senator MURRAY. I appreciate it. As some of you know, traveling 3,000 miles to get to a hearing is a large undertaking. These people have made a tremendous effort. So, I appreciate your allowing them in.

I just have one question for Dr. Klausner. I know we have a number of other panels.

I am delighted we have been joined by Senator Mikulski who has been such a great, great advocate for these issues for a long time. I will just ask one so she can get to hers.

I just wanted to ask about one of the contentious issues that is contained in the McCain-Edwards-Kennedy Patients' Bill of Rights that we have been discussing on the floor of the Senate, and that is access to clinical trials and innovative new treatments. Some of the opponents of the legislation have been arguing that access to clinical trials is too costly. It seems to me that if we save lives and move forward, that those costs are offset.

But could you just talk for a minute about how important clinical trials are in treating blood-related cancers?

Dr. KLAUSNER. Yes, I feel very passionate about this. All of the progress we have made, when we have made progress, is the result of clinical trials. We will not make progress without clinical trials. I think it is wrong and unfair to deny patients access to clinical trials.

But we have also studied this issue whether care in the context of a cancer clinical trial is more expensive than care outside the clinical trial. We have done at least four studies. We are waiting for a much larger study we have done with the RAND Corporation, and every study shows that there are no significant added clinical costs. So, I think the cost argument is unacceptable, and I think we need to move to make sure that patients are not denied that opportunity for themselves as well as to contribute to society at large.

Senator MURRAY. Thank you very much. I appreciate that response.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you very much, Senator Murray.

Senator Mikulski.

STATEMENT OF SENATOR BARBARA A. MIKULSKI

Senator MIKULSKI. Thank you very much, Mr. Chairman. First of all, let me thank you for affording me the courtesy of participating with this subcommittee. Though I am an appropriator, I am not a member of this subcommittee.

I hope though, as the chair of the VA/HUD appropriations subcommittee, that we could have lessons learned from this hearing on how there could be applicability for the information in veterans' health care, in terms of detection, treatment, and certainly on VA clinical research.

I am here because I want to learn. I am a very proud cosponsor of the Hutchison bill. I want to learn because, like all of us, we come because it affects people in our family. A very close member of my family is Geraldine Ferraro. I regard her like a sister, and when I heard of this information and her situation, I was determined to work on a bipartisan basis on this.

I know that we are going to hear testimony from Mr. Larry Lucchino, who used to be in Baltimore with the Orioles and now is CEO with the Padres. We went out in Little Italy together. We drank wine.

I even took him to an inaugural dance, and here we are. But he has gone on to another life and love. And, well, I am an appropriator.

So, I am just happy to be here. I am going to waive my questions to Dr. Klausner. We meet often and talk, and I know the subcommittee is running late.

But, again, thank you so much and I will have other questions.

Senator HARKIN. Thank you very much, Dr. Klausner, for everything. We will dismiss you and we will bring up the next panel: Dr. Sandra Horning, Mr. Larry Lucchino, Dr. Hagop Kantarjian, Mr. Miles Pendleton, Jr.

Because of the tightness of time—11:30 we have a full committee hearing that we must tend to—I am going to ask if each person can just try to limit it to 4 minutes. I am going to try to get this timer light, if I could. I hate to do that, but it is just simply a time problem. We will move ahead as aggressively as possible.

When you finish, if you could come up here and sit someplace. Those of you in back, we have some empty seats up in front. So, those who may really need to sit down, please come up here and take some of the seats.

So, we will start with Dr. Sandra Horning, Professor of Medicine, Stanford University, a member of the Board of Directors of the American Society of Clinical Oncology, and as I said, from my back yard of Creston, Iowa. Dr. Horning.

STATEMENT OF SANDRA J. HORNING, M.D., STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. HORNING. Thank you. As stated, I am a professor of medicine at Stanford University where I do clinical research in Hodgkin's disease and non-Hodgkin's lymphoma. I am also pleased to serve on the Scientific Advisory Board of the Cure for Lymphoma Foundation and also as a member of the Board of Directors of the American Society of Clinical Oncology.

Mr. Chairman, I would like to thank you and your colleagues, Senator Specter and Senator Hutchison, for your leadership in scheduling this timely hearing upon the release of the Leukemia-Lymphoma-Myeloma Progress Review Group report. As you have heard we are currently poised to make significant advances in the treatment of blood-related cancers. I am especially honored to appear before a fellow Iowan with a strong commitment to biomedical research, and as this represents my own 5-year survivorship of malignancy, I also identify strongly with the large number of advocates present here today.

Lymphoma, as you heard, with some introduction from Dr. Klausner, is a general term for cancer of the lymphatic system, which is part of the immune system. There are two-broad based categories of lymphoma, the relatively common non-Hodgkin's lymphoma, which I will refer to as lymphoma and the more rare Hodgkin's disease.

From 1973 to 1998, the incidence rate for lymphoma increased by 83 percent with the current estimate of more than 56,000 cases annually. This is actually the highest rate of increase for any cancer, an increase that is unexplained. Further, lymphoma represented the second greatest increase in mortality among all cancers over the same period. The success of treatment varies with an overall 5-year survival rate of 54 percent.

The lymphomas are complex disorders with more than 30 unique subtypes. As you have heard, molecular profiling of the lymphomas is now underway on a large scale. This work promises great benefits for diagnosis and new targets for therapy, but it also poses a significant challenge, the challenge inherent in conducting clinical research for rare diseases.

There is great enthusiasm for the new immunotherapies modeled after the body's own immune system that are revolutionizing the treatment of lymphoma. The monoclonal antibody Rituxan targets the marker on the surface of 80 percent or more of the lymphomas. Because antibodies like Rituxan have few side effects, they are favored by patients and they can be combined with chemotherapy or radiation therapy.

Several new antibodies that target different markers expressed on lymphoma cells are being tested currently in clinical trials. Antibodies can also be used as a targeted delivery system for toxins or radiation. Two new products, Bexxar and Zevalin, combine a radioisotope with an antibody targeted to B-cell lymphoma. Promising data from clinical trials has been reported with both.

Recent technological advances have made it possible to custom-make vaccines for B-cell lymphoma on a scale sufficient for testing in large clinical trials. These vaccines are designed to stimulate an anti-lymphoma effect among patients in remission after chemotherapy, but destined to relapse after conventional treatment.

Discoveries in lymphoma and other hematologic cancers have often blazed the trail for the common solid tumors, and it is our belief that the pioneering development of immunotherapy for lymphoma will also lead to improved treatments in other cancers.

I see my light is turning red.

I want to put a plug in for the integral role of clinical research that has been mentioned. It represents a major success of the fed-

erally supported cancer program. However, clinical research in rare diseases can be a daunting task due to the time and costs involved. The participation of community oncologists is absolutely critical to timely and full accrual to clinical studies in lymphoma and Hodgkin's disease. Thus, appropriate allocation of resources to the design, organization, and execution of clinical research in the community is needed.

The NIH and the pharmaceutical industry are important partners in drug development and clinical research. We believe for that reason that the Patients' Bill of Rights must include comprehensive coverage of cancer clinical trials, coverage that would ensure access to both FDA-sponsored and Government-funded trials.

On behalf of all of us who are passionate about understanding and effectively treating the hematologic cancers, researchers, the 700,000 patients who currently have these diseases, and their practitioners, I would like to thank you for holding this hearing. The hematologic cancers pose serious challenges and offer unprecedented opportunities.

May I just have 30 more seconds?

Senator HARKIN. Yes.

Dr. HORNING. Thank you.

PREPARED STATEMENT

So, our recommendations are to implement the recommendations of the Progress Review Group, to heighten efforts to identify the reasons for the increased incidence of lymphoma, to improve coordination among the NCI, FDA, and the pharmaceutical industry, and enactment of the Patients' Bill of Rights with comprehensive clinical trials coverage.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF SANDRA J. HORNING

Good morning, I am Dr. Sandra J. Horning, Professor of Medicine at Stanford University School of Medicine. My clinical research in Hodgkin's disease and non-Hodgkin's lymphoma (NHL) focuses on improving therapeutic outcomes, reducing treatment complications, and elucidating the biology of the diseases. I am also pleased to be here today in my capacity as member of the Scientific Advisory Board of the Cure For Lymphoma Foundation, an organization that supports lymphoma research and education, and as a member of the Board of Directors of the American Society of Clinical Oncology (ASCO), the world's leading medical specialty society for cancer researchers.

Mr. Chairman, I would like to thank you and your colleagues, Senator Specter and Senator Hutchison, for your leadership in scheduling this hearing on hematological cancer research. This hearing is timely because the report of the Leukemia-Lymphoma-Myeloma Progress Review Group (LLM–PRG) has just been published and because we are poised to make significant advances in the treatment of blood-related cancers. We welcome the opportunity to review recent research progress and consider policy changes that might accelerate the development of new treatments for these cancers.

As a native of Creston, Iowa and graduate of the University of Iowa School of Medicine, I am especially honored to appear before a fellow Iowan. Your strong commitment to biomedical research has ensured that we have the financial resources to support basic biomedical research and to expand the clinical trials network of the National Cancer Institute (NCI) across the nation. A balanced approach of support for basic and clinical research is essential to achieving improvements in the treatment of all cancers.

A LYMPHOMA PRIMER

Lymphoma is a general term for cancer of the lymphatic system, which is part of the immune system. There are two broad categories of lymphoma, one relatively common—non-Hodgkin's lymphoma, or NHL, and one relatively rare—Hodgkin's disease. There are approximately 64,000 cases of NHL and 7,400 cases of Hodgkin's disease diagnosed annually in the United States. Taken together, lymphomas rank as the fifth most common cancer behind prostate, breast, lung, and colorectal cancer.

The non-Hodgkin's lymphomas (NHL) are categorized based on their appearance under the microscope and their expression of immune system markers, which allows them to be classified as originating from B- or T-cells. These are complex disorders, with more than 30 unique subtypes. Some NHL grow and spread quickly, whereas others develop more slowly. Thus, the NHL have been broadly characterized as aggressive or indolent. Utilizing current technology to assess the expression of many genes, potential new subtypes of NHL have been identified based on molecular "profiles."

Between 1973 and 1998, the incidence rate for NHL increased by 83 percent, the highest rate of increase for any cancer. Although occupational exposure to chemicals has been implicated, the increased incidence of NHL is unexplained. The importance of NHL is highlighted by the fact that this disease also represented the second greatest increase in cancer mortality over the same period. The treatments for NHL include radiation, chemotherapy; stem cell transplantation; and immunotherapy. The success of treatment varies according to NHL subtype and clinical features, resulting in a collective five-year survival rate of only 53 percent.

In contrast, the incidence of Hodgkin's disease has been stable and the five-year survival rate has improved steadily to the current figure of 85 percent. However, Hodgkin's disease remains a very important disorder because the young patients with this disease, median age less than 30 years, may have serious long-term adverse effects, such as second cancers, as a result of chemotherapy and radiation treatments. Studies of risk assessment, risk reduction and prevention are critical not only to the long-term survivors of Hodgkin's disease but for all cancer patients treated with chemotherapy and radiation therapy.

LYMPHOMA SUBTYPES

Significant insights into the underlying biology of the NHL have resulted from recent research efforts. In work that Dr. Richard Klausner has already described, researchers at the NCI, Stanford, and the University of Nebraska and other institutions utilized microarray technology to assess gene expression in the most common NHL subtype, diffuse large B-cell lymphoma.

This research suggested that the clinical behavior of diffuse large B-cell lymphoma corresponds to the expression of genes in the immune cell of origin, such that two distinct diseases were identified. For patients with one subtype, roughly three-quarters were alive five years after chemotherapy, whereas less than one-quarter of those with the other subtype were alive five years after treatment.

Currently, molecular profiling of lymphomas and leukemias is underway on a much larger scale. This work promises not only to help determine prognosis for individual patients but to provide new therapeutics targeted to the underlying biology. Ultimately, research initiatives will be more focused, physicians will assist patients in making more informed decisions, and the survival of NHL patients will improve.

Although molecular sub-typing of NHL will surely yield important benefits, it also poses significant research challenges. The further sub-classification of NHL changes a collectively common cancer into many orphan diseases, with all the challenges inherent in conducting clinical research for rare disorders. The same circumstance will ultimately be true of the most common cancers as their biology is further understood. Thus, it is important to address this challenge with the NHL here and now.

CURRENT TREATMENT OPTIONS AND TREATMENT ADVANCES

Treatments for NHL have traditionally included chemotherapy and radiation therapy. For those with recurrent lymphoma, high dose chemotherapy or radiation with stem cell transplantation may be a treatment option.

New immunotherapies, modeled after the body's own immune system, are revolutionizing the treatment of NHL. A monoclonal antibody called Rituxan is approved for the treatment of recurrent, indolent B-cell non-Hodgkin's lymphoma. Rituxan targets a B-cell antigen, CD20, found on normal and malignant B-cells. (Because the youngest B cells do not express the CD20 antigen, normal B-cells regenerate after treatment). In addition to killing lymphoma cells by traditional immune mechanisms, Rituxan may send a direct death signal. Most exciting, antibodies like

Rituxan have few side effects, allowing their combination with chemotherapy or radiation therapy. Some studies already demonstrate a benefit for such combinations compared with conventional therapies.

Several new monoclonal antibodies that target different antigens expressed on B- and T-cells are being tested in clinical trials. These new therapeutics create the possibility of "combination immunotherapy." Antibodies can also be used as a targeted delivery system for cell toxins or radiation. Bexxar and Zevalin are two products in advanced stage of development that combine a radioisotope with a monoclonal antibody targeted to the CD20 antigen of B-cells. Promising data from clinical trials has been reported with both of these new agents.

Vaccines derived from the B-cell antigen that is unique to an individual's NHL have been applied after conventional chemotherapy for indolent lymphoma. Recent technological advances have made it possible to "custom make" these vaccines on a scale sufficient for testing in large clinical trials. Based on preliminary studies, researchers hope these vaccines will have an anti-lymphoma effect for patients with minimal disease or in remission but destined to relapse after conventional treatment.

It is our hope that these immunotherapies, used as a complement to other therapies or in combination with other therapies, will significantly and favorably impact the survival rates for NHL. In addition to their therapeutic promise, immunotherapies have fewer and less severe side effects than those of chemotherapy and radiation.

The moderation or elimination of the serious side effects of treatment is of great concern to patients. As mentioned, success in treating Hodgkin's disease has been accompanied by serious adverse effects, including second cancers, sterility, organ dysfunction, and psychosocial effects, all of which impact quality of life. It is imperative that we strive not only for cures, but also for the least complicated cures, in our research efforts.

Discoveries in lymphoma and other hematological cancers have often blazed the trial for the common solid tumors, and it is our belief that the pioneering development of immunotherapy for lymphoma will also lead to improved treatments in other cancers.

CHALLENGES FOR CLINICAL RESEARCH IN LYMPHOMA

The integral role of clinical research in patient care represents a major success of the federally supported cancer program. In a 1998 ASCO (American Society of Clinical Oncology) survey, more than 80 percent of physicians indicated that they enroll patients in clinical trials. The active participation of the academic and community oncologist in clinical research is essential for the rapid clinical testing of promising new therapies. Patients often make decisions about enrollment in clinical trials, which may represent the best treatment option, in consultation with a community oncologist.

Despite the enthusiasm among oncologists regarding clinical research, there are obstacles to participation that result in a small percentage of eligible patients who actually enroll in clinical trials. The ASCO study of clinical trials uncovered serious strains in this system, including the fact that oncologists often receive inadequate reimbursement for the costs of enrolling patients in clinical trials. In addition to the added time to inform and consent patients, fixed costs associated with enrolling patients in trials include the approval of trials by an institutional review board (IRB), data management requirements during and after treatment, and the reporting of adverse events.

These obstacles become more daunting in rare disorders, where the time and costs may prove overwhelming for busy practitioners. As we move toward the subclassification and further sub-classification of cancer, first with the NHL and later with other cancers, these issues must be addressed in order to promote clinical trials of new therapies. The participation of community oncologists is absolutely critical to timely and full accrual to clinical studies in NHL and Hodgkin's disease. Thus, appropriate allocation of resources to the design, organization and execution of clinical research in the community is needed.

ROLE OF INDUSTRY IN CLINICAL RESEARCH

Support of basic biomedical research and a nationwide clinical trials network by the National Institutes of Health (NIH) and support of clinical research by the pharmaceutical industry represents an important partnership. The pivotal trials of new agents are often conducted exclusively by industry, with Rituxan and Gleevec as recent examples. Subsequently, important trials for new indications of approved drugs

frequently emanate from the cooperative groups, as evidenced by multiple ongoing trials incorporating Rituxan in NHL.

The translation of basic research into new NHL treatments occurs in academic research centers like Stanford (usually the result of NIH funding), small biotechnology companies, and large pharmaceutical companies. The new immunotherapies—Rituxan, Bexxar, Zevalin, as well as new lymphoma vaccines—represent the results of this partnership.

Both patients and physicians prize access to industry-sponsored trials. For patients, they often represent the only avenue to potentially life-extending new agents. Physicians wish to offer their patients novel therapies at the earliest possible time. Industry trials are attractive because they are designed and conducted with a sense of urgency, leading to timely results. Significantly, industry trials pay for enrollment of patients at a rate that approximates the actual cost of necessary clinical trial activities. In contrast, the ASCO study found that reimbursement rates for these activities in NCI-sponsored trials were well below the actual costs incurred by physicians.

Thus, industry-sponsored trials play an essential part in the overall clinical research enterprise and should not be considered of lesser significance than trials sponsored by NIH. It is for this reason that the cancer community has advocated a clinical trials coverage provision in the various Patients' Bills of Rights that would ensure access to industry-sponsored as well as government-funded trials. When Congress eventually passes a Patients' Bill of Rights, it must include comprehensive coverage of cancer clinical trials.

RESEARCH RECOMMENDATIONS OF THE LLM–PRG

Researchers and advocates commend the NCI for convening the Leukemia, Lymphoma, and Myeloma Progress Review Group (LLM–PRG), comprising more than 180 researchers, clinicians, patient advocates, industry representatives, and government officials. In May 2001, this group released its evaluation of research on hematologic malignancies.

One of the most important benefits of the PRG process is its inclusion of advocates in the deliberations. Advocates brought to the PRG deliberations a sense of urgency and an insistence on removal of bureaucratic barriers to the development of new therapies.

The core recommendations of the PRG relate to methods for shortening the time for translating basic research findings into new treatments. Among the research and development strategies identified in the PRG report are:

—Fostering partnerships among NCI, academics, advocates, cooperative groups, the Food and Drug Administration (FDA) and industry;

—Developing education and training programs for certification of physicians and centers for diagnosis, treatment, and clinical trials in hematological malignancies

—Establishing innovative new research mechanisms to foster collaboration among experts from multiple disciplines and institutions.

New treatments, in many cases, may be integrated with established treatments. Appropriate allocation of resources to the design, organization and execution of clinical research in the community is needed to study the resultant, multiple combinations and permutations. The advocates emphatically endorse improved communication between physician and patient regarding increasingly complex treatment decisions. Further, the advocates strongly support research efforts directed toward the late effects of treatment.

RECOMMENDATIONS FOR CONGRESSIONAL ACTION

On behalf of all of us who are passionate about understanding and effectively treating the hematologic cancers—patients, researchers, and practitioners—I would like to thank you for holding this special hearing to consider the state of their research.

The hematological cancers pose serious challenges and offer unprecedented opportunities. The incidence of NHL is increasing for reasons that we do not understand and the five-year survival rates for NHL, myeloma, and leukemias remain unacceptably low. Breakthroughs in molecular diagnostics promise new, targeted treatments based on increased understanding of the biology of these diseases. Meanwhile the era of specific immunotherapy has begun with resounding success and we see much more on the horizon. In order to accelerate the realization of these unparalleled opportunities, we recommend several actions by Congress to improve the environment for research on lymphoma and the other blood-related cancers:

—Implementation, facilitated by the NCI, of the collaborative strategies for research and development of hematological cancer therapies recommended by the LLM–PRG;
—Heightened efforts to identify the reasons for the increased incidence of lymphoma; Improved coordination among NCI, FDA, and industry to bring new drugs to market sooner;
—A system of payment for enrolling patients in lymphoma clinical trials commensurate with their complexity and costs; and
—Enactment of a patients' bill of rights with comprehensive clinical trials coverage, including industry-sponsored trials under regulatory authority.

This is an exciting time to be involved in research on hematological cancers. I would again like to express the deep appreciation of the research community for the strong Congressional support for biomedical research. We look forward to a continued strong partnership, advancing our understanding of cancer, developing new therapies, and rapidly testing these new treatments in patients, continually striving for cures with the best quality of life.

Senator HARKIN. Thank you very much, Dr. Horning. I had to cut you off. They would think I was playing favorites if I let you go on.

Mr. Lucchino.

STATEMENT OF LARRY LUCCHINO, PRESIDENT AND CEO, SAN DIEGO PADRES

Mr. LUCCHINO. Yes, good morning. I am Larry Lucchino. I am the president and CEO of the San Diego Padres. I speak to you today as a survivor of non-Hodgkin's lymphoma in the 1980's and prostate cancer in the 1990's. I would like to thank you as well for the opportunity to discuss my experiences and to highlight the need for strong Federal support for biomedical research.

Senator Harkin, I would like first to thank you and to thank Senator Specter, Senator Hutchison, Senator Murray, and my old, dear friend, Senator Mikulski, for your strong interest in leukemia, lymphoma, and myeloma. These diseases have been too long off the radar screen. As a Pittsburgh native, I would especially like to salute Senator Specter from my home State for his leadership in the fight for biomedical research.

In the fall of 1985, I was diagnosed with non-Hodgkin's lymphoma. I was told the odds were very much against me. I went to a physician to determine the source of a persistent cough and was given a life-altering diagnosis. I was told only one-third of us would survive. Fortunately, I was referred to the great Tom Fry and the Dana-Farber Cancer Institute in Boston where I underwent aggressive chemotherapy and an autologous bone marrow transplant. As I recall, I was only the 33rd patient to receive this treatment at Dana-Farber. Bone marrow transplantation, an experimental for lymphoma 15 years ago, is now considered standard treatment around the country for thousands of lymphoma patients.

Almost a decade and a half after that experience, the numbers on non-Hodgkin's lymphoma do not tell a promising story. As Dr. Horning referred to, between 1973 and 1998, the incidence rate for non-Hodgkin's lymphoma increased almost 83 percent. The 5-year survival rate for non-Hodgkin's lymphoma still hovers at about 54 percent. For those who are treated successfully, the long-term side effects can be devastating.

I applaud the NCI for convening its blue ribbon panel to review the current program on lymphoma, leukemia, and myeloma and proposing new strategies for accelerating the translation of basic research findings into new treatments. My own physician, the ines-

timable Dr. Lee Nadler of Dana-Farber, was a member of that group, so I know it took an aggressive approach.

My message today is simple. We must accelerate the research and development process, and we need to do it now. For those of us who have been diagnosed with cancer, time is a precious commodity. We believe that old structures must be reformed and new systems created to bring treatments to patients at a faster pace. The time and distance from a scientist's laboratory bench to the patient's bedside must be shortened.

The NCI's blue ribbon panel specifically emphasized collaboration and cooperation among researchers, industry, Government, and advocates. I would like to specifically acknowledge the contribution of the Cure for Lymphoma Foundation, a private organization that funds research, as an example of the partnership that will be critical to moving the research agenda forward.

More specifically I would like to recommend some concrete action steps.

Please maintain a strong Federal role in the funding of biomedical research.

Please implement a balanced approach of support for basic and clinical research so that laboratory discoveries can be translated quickly.

Please develop a budget for the recommendations included in the PRG panel and hold the NCI accountable for implementing that research plan.

Please encourage additional collaboration between the private and the public sectors, between industry, academia, and the Government. We need a new alliance.

Please implement on a pilot basis new methods for evaluating and collaborating in research.

Senator SPECTER [presiding]. Mr. Lucchino, I am very reluctant to interrupt anyone, especially an ex-Pennsylvanian.

But we are on a very tight time table and have to be at a markup on the supplemental. So, we are going to have to ask you to take 30 more seconds.

Mr. LUCCHINO. I will do so. Thank you.

Senator SPECTER. We are going to have to ask everybody else to observe the red light meticulously. Thank you.

PREPARED STATEMENT

Mr. LUCCHINO. I would like to make perhaps a reference to the sports world in which I operate these days. It is a real privilege and I think a duty for someone in the toy department of life, the world of baseball, to come and have a chance to contribute to issues as important to all of this. Perhaps I can take from the sports world an expression, if Nike will excuse the borrowing. Life is short; research hard.

Thank you very much for this opportunity.

[The statement follows:]

PREPARED STATEMENT OF LARRY LUCCHINO

Good morning, I am Larry Lucchino, President and CEO of the San Diego Padres. I speak to you today as a survivor of non-Hodgkin's lymphoma in the 80's and prostate cancer in the 90's. I would like to thank you for this opportunity to discuss my

experiences and to highlight the need for strong federal support for biomedical research and innovative strategies for public and private research partnerships.

Senator Harkin, I would like to express my appreciation to you, Senator Specter, and Senator Hutchison for your strong interest in cancer research and your willingness to hold this special hearing focusing on leukemia, lymphoma, and myeloma. As a Pittsburgh native, I would especially like to salute the senior Senator from my home state of Pennsylvania, Senator Specter, for his leadership in the fight for federal funding for biomedical research.

TREATMENT FOR NON-HODGKIN'S LYMPHOMA

When I was diagnosed with non-Hodgkin's lymphoma in the fall of 1985, I was told that the odds were very much against me. I went to a physician to determine the source of a persistent cough and was given a life-altering diagnosis. Fortunately, I was referred to the great Dana-Farber Cancer Institute in Boston, where I underwent aggressive chemotherapy and an autologous bone marrow transplant. As I recall, I was only the 33 patient to receive this treatment at Dana-Farber. Bone marrow transplantation, an experimental treatment for lymphoma 15 years ago, is now considered standard treatment for certain lymphoma patients.

Just two years ago, I was diagnosed with prostate cancer and underwent treatment at Johns Hopkins. I will focus my remarks today on lymphoma and the other blood-related cancers, but the research strategies and public policies that will make a difference for lymphoma patients will also make a difference for prostate cancer patients and all other cancer patients, as I understand that discoveries in lymphoma have frequently pioneered advances in other cancers.

The numbers on NHL do not tell a promising story. Between 1973 and 1998, the incidence rate for non-Hodgkin's lymphoma increased almost 83 percent, among the highest rate of increase for any cancer. For that same time period, the death rate for NHL increased by 45 percent. Although significant progress has been made in treatments for some cancer, including Hodgkin's disease and certain childhood leukemias, the five-year survival rate for non-Hodgkin's lymphoma still hovers at about 54 percent. Even for those who are treated successfully, the long-term side-effects can be devastating.

The challenges are obvious. We must still answer fundamental questions about the causes of NHL and at the same time accelerate the pace of development for new treatments.

ADVANCES IN LYMPHOMA RESEARCH

In the last several years, there have been some important developments in the treatment of NHL. The most promising broad category of treatments are those that are referred to as immunotherapies, or therapies that utilize the body's own immune system to fight cancer. A monoclonal antibody has been approved for the treatment of a form of B-cell lymphoma, and radioimmunotherapies, which combine monoclonal antibodies with radiation, are in development for the same type of lymphoma. Monoclonal antibodies for additional forms of lymphoma are being investigated, and researchers are designing and testing vaccines, which are created for each individual from the tissue from his or her tumor.

There is great hope that these treatments will improve the outlook for lymphoma patients, but it is still too soon to know if they will have a significant impact on the lymphoma survival rate.

CONVENING OF A BLUE RIBBON PANEL

The National Cancer Institute (NCI) deserves commendation for convening a blue ribbon panel to review its current program of research on lymphoma, leukemia, and myeloma and to propose new strategies for accelerating the translation of basic research findings into new treatments. I was not a participant in this group, but I was pleased to learn that cancer survivors like myself were an integral part of the deliberations and that my own physician, the inestimable Dr. Lee Nadler of Dana-Farber Cancer Institute, was a member of the group.

I have read the recommendations of the blue ribbon panel, and I believe they point us in an important direction for hematological cancer research. However, I would like to echo a theme that was central to the report, a theme that I imagine was pressed by the cancer survivors and other advocates: accelerate the research and development process. And please do it now!

For those of us who have been diagnosed with cancer, time is a precious commodity. We believe old structures must be reformed and new systems created to bring treatments to patients at a faster pace. The report emphasizes collaboration

and cooperation among researchers, industry, government, and advocates to achieve this goal.

I would like to acknowledge the contribution of the Cure For Lymphoma Foundation (CFL), a private organization that funds research and supports educational and informational programs for physicians, researchers, patients, and their families. CFL and other private organizations like it make a valuable contribution to the field, and their financial resources are an important complement to federal research funding. This is but one example of the partnership that will be critical to moving the research agenda forward.

ACTION ON THE RECOMMENDATIONS

I would like recommend some concrete action steps if I may:

1. Maintain a strong federal role in the funding of biomedical research. The Congress and Bush Administration have committed to doubling the budget between 1999 and 2003, but there appears to be no plan beyond that time. To prevent disruption in research and sustain the progress we are making, Congress and the Administration must develop and endorse a funding strategy beyond 2003.

2. Implement a balanced approach of support for basic and clinical research so that laboratory discoveries can be translated into improved patient outcomes.

3. Develop a budget for the recommendations included in the Blue Ribbon Panel, and hold the NCI accountable for implementing the research plan offered by the leaders in lymphoma, leukemia, and myeloma research.

4. Encourage additional collaboration between the private and public sectors. At present, new drug development is, at least initially, almost exclusively the domain of pharmaceutical and biotechnology companies. Basic science discoveries made in publicly funded laboratories in academia and the National Institutes of Health (NIH) could be translated by industry into clinical applications more quickly if the flow of information were more efficient. This should be a priority of NIH in order to ensure that the public benefits from the nation's research investment at the earliest possible juncture.

5. Implement on a pilot basis, with rigorous methods for evaluation, new structures for collaborative research. The patient advocates in the PRG were captivated by the concept of a multi-institutional and multi-disciplinary consortium that would accelerate the drug development process. The Chronic Lymphocytic Leukemia Research Consortium, centered at one of my favorite institutions, the University of California at San Diego, may serve as a model for the kind of collaboration involving researchers from different fields and different institutions.

I was a healthy young man when I was diagnosed with non-Hodgkin's lymphoma. Since my initial diagnosis, many more in the world of sports have been diagnosed and treated for cancer, hockey players Mario Lemieux and John Cullen, golfer Arnold Palmer and cyclist Lance Armstrong. The first reaction for many of us was a desire to understand why we had cancer, but for some of us that initial instinct has developed into activism aimed not only at answering why we were diagnosed with cancer but also aimed at educating the public about cancer, solidifying support for federal funding of biomedical research, and improving the environment for private sector research efforts. It is my honor to be here with you today and to join with other advocates in support of bold and creative approaches to cancer research. To paraphrase an expression from the world of sports advertising, " Life is short; research hard (and fast)." Thank you.

Senator SPECTER. Thank you very much, Mr. Lucchino.

Senator Harkin has had to leave us for other commitments, and he has left the gavel in my hands.

STATEMENT OF MILES S. PENDLETON, JR.

Senator SPECTER. We turn now to Mr. Miles Pendleton, a retired Foreign Service Officer, diagnosed with CLL leukemia in 1989 while serving in London. Mr. Pendleton is a graduate of Yale, Harvard, and the National War College. Thank you for joining us, Mr. Pendleton, and we look forward to your testimony.

Mr. PENDLETON. Thank you very much, Senator Specter. I appreciate it.

I will not describe the disease. Think of CML without a cure. Think of lots of us having pretty ugly chemo and experiences that

you can all imagine that go with it. From looking at me, you can tell that I am perhaps a lucky person. This room is full of courageous blood disorder patients who are worse off than I am. Despite being heavily treated over the years, I am determined to beat back this dragon with the help of all of those who are doing CLL research. In the process, no institution is more central than NCI and no army in the field is more important than the recently established CLL Research Consortium, which needs a higher level of funding now.

When I was first told that I had leukemia, I was running the political section in London and I was called out of a meeting, and a doctor told me on the phone, Mr. Pendleton, you have leukemia, but it is chronic. It is the good kind.

Members of the committee, I can assure you there is no good leukemia. I can also assure you that having leukemia is not career-enhancing.

We are all encouraged to take a tape recorder to the first meeting with the doctor who diagnoses us and invites us to come in for a little chat about our blood tests. That is because after we hear the word "leukemia," we are not going to remember a thing. I can guarantee you. Try it sometime.

A few words about CLL and the effort to cure it, particularly through the Research Consortium funded by NCI. CLL is the most common form of adult leukemia. More voters in your States have it than any other form of leukemia. There are about 100,000 of us alive today. Nobody knows what triggers it, and so there is not yet a Gleevec, but we are on the march. Nobody knows what to target. Unfortunately, because of the toxins, we are not living any longer than when I graduated from college 10 years ago—40 years ago.

I was just back at my reunion and it seems like 10.

It really destroys your life in many ways, a lot like AIDS.

But there is an accelerated measure of hope on the research front through the consortium which brings together in an unprecedented way institutions from Boston to La Jolla. It is funded with a $16.5 million grant which sounds like a lot, but it is split amongst nine institutions and to be spent over 4 years. Basically that ain't much. It is about what was spent by Mrs. Casey to buy the site for the new mayor's residence here in Washington.

To my astonishment, the consortium is unique in that for the first time in NCI history it brings together the top researchers from places like the Dana, from places like M.D. Anderson. They are really making headway.

Senator SPECTER. Mr. Pendleton, the red light has been on. Would you summarize please?

Mr. PENDLETON. Yes. I will quote you.

Senator SPECTER. Take all the time you need.

Mr. PENDLETON. You once said that druthers do not dollars make. The consortium needs more dollars. It needs about $20 million now.

Thank you, Senator.

Senator SPECTER. Thank you, Mr. Pendleton.

We had a sense of a Senate resolution which expressed druthers, but they do not translate to dollars. So, I think that is where it ought to be identified.

PREPARED STATEMENT

Mr. PENDLETON. Well, there is some report language out there too which are druthers.

[The statement follows:]

PREPARED STATEMENT OF MILES S. PENDLETON, JR.

Thank you Senator Harkin, Senator Specter, and members of this Committee for inviting me to appear today. Right at the outset, I want to say how much millions of patients and our families appreciate what this Committee has done over the years for patients, medicine and medical research.

My name is Miles Pendleton. For three decades I was a U.S. Foreign Service Officer serving in the Department of State and in embassies abroad. I visited with members of the Senate and House on many occasions, both formal and informal. But, frankly, I am not entirely happy to be appearing before you today because I do so as a leukemia patient—no matter how robust I may appear at the moment.

I have long had and been treated for Chronic Lymphocytic Leukemia, known as CLL. This is not CML, the chronic leukemia that may be cured by the recently approved and much heralded pill called Gleevec. In CML the target is known. In CLL it is not. I will focus on CLL.

In CLL patients, our bodies produce abnormal lymphocytes, a subtype of white blood cells that migrate to the lymph nodes or other lymphoid organs. They clog the body, crowding out the good cells in the blood and marrow. They are relentless and refuse to die.

This is happening to my body, which is also residually impregnated with a decade of toxins from oral chemo and infusions through the arm that kill good and bad cells alike. As we say in the Foreign Service, this is not "career enhancing".

Mr. Chairman, as you know, this room is full of blood disorder patients, many who have come to Washington under the new umbrella of Leukemia, Lymphoma, Myeloma-ACT to lobby for more research funding for blood disorders. Many in this room are worse off than I am. I was diagnosed years ago, in 1989, and despite many ups and downs, am still kicking with a measure of ferocity. I can commiserate totally with fellow patients who have engaged in bigger, more immediate, and more desperate battles. In particular, I am in pain to find that that distinguished American, Geraldine Ferraro, has reason to testify as a patient today. She is an inspiration.

To many with CLL and other blood disorders, a twelve-year survival must seem like a dream come true. It is. But I have had my turn at harsh treatments with the resulting nausea, fatigue and mental disorientation. Last time, it got bad enough that I could not ride on the Washington Metro because the smell of the seats reminded me powerfully of the chemo infusion chair. I will have my turn at heavy treatment soon again—my turn to fight directly with what that remarkable patient and CLL activist Barbara Lackritz calls "our dragon".

I am determined to beat it back over and over again with the help of all those who are doing CLL research, not only in the United States but in the world. In that process, no institution is more central than the National Cancer Institute, and no army in the field is more important that the groundbreaking CLL Research Consortium, which needs a higher level of funding now.

Let me tell you how I was told I have leukemia. At that time, I was running the Political Section at the U.S. Embassy in London and complaining of fatigue that led to a blood test. I was called out of a meeting on the Human Rights Report to take a call from a doctor who said—on the phone and all too briefly—that I had leukemia. But the "good" chronic kind. I should see a specialist. Soon I was told I could expect to live five years or more. I heard five years. One of my colleagues later told me that I seemed a bit disoriented when I returned to the meeting. I did not tell him or anyone else but my wife about the diagnosis.

I was 48. My wife and I suddenly had to ponder all those questions about the future of our family and careers as we faced my mortality. You can imagine what issues arise. If you can't, ask any one of many patients in this room. We are all encouraged to take a tape recorder to the first meeting with the doctor who diagnoses us and invites us to come in for a little chat about out blood test—if we are not told on the phone. That is because after we hear the word "leukemia," we generally will not remember a thing.

Mr. Chairman, you will recall that I was told I have a good leukemia. There is no good leukemia or any other blood disorder. There is no good cancer. As a doctor said at a conference at the National Cancer Institute last week, the only good cancer

cell is a dead cancer cell. Another doctor told me that I am a lucky patient. And of course I am. The fact that I am very much alive and generally thriving at age 62 means that I have not faced the ultimate immediacy of death that Representative Joe Moakley bore with such grace and dignity.

Allow me to say a few more words about CLL and the effort to cure it, particularly through the CLL Research Consortium funded by NCI—and all the intramural and extramural research and researchers who are working throughout the country and around the globe. As you listen to these words about one subset of leukemia, CLL, please multiply by many fold the impact on patients, families and the economy of blood disorders and other forms of cancer.

CLL is the most common form of adult leukemia in the United States and in the western world. More voters in each of your states have this form of leukemia than any other. In the United States somewhat under 10,000 people are diagnosed with CLL each year, and 5,000 die. There are about 100,000 of us alive at any given time. More men than women, but women are hardly excluded. Unlike CML, nobody knows what triggers CLL. Nobody really knows what to target, but CLL researchers are getting closer every day. There are increasing indications that environmental factors play a role in the process, causing abnormalities in genes.

To date, CLL can not be cured. Indeed, those of us with CLL are not living any longer in the aggregate than when I graduated from college 40 years ago. And this is despite intensifying and gratifying research efforts and new but risky ways of managing the disease. For instance, we have all heard about bone marrow transplants, but unfortunately almost one quarter of those going the transplant route using marrow from matching siblings are dying, usually from graft-versus-host disease following the procedure.

Clearly CLL needs a Gleevec. We need a Gleevec in less than the 40 years it took to develop that drug. Breakthroughs may be near. We need to know first what to target. And fortunately some extraordinary genetic work is being done under the leadership of NCI and the CLL Research Consortium in an effort to identify subgroups, targets and cures like Gleevec. (Incidentally, Medicare will not cover Gleevec as a pill. Only as an infusion via a vein. Legislation is needed to change that, and it is needed now.)

CLL is not unlike AIDS in the way it destroys patients' health and lives. It is quite parallel to the notion of starting with HIV and then becoming full blown. The median age of diagnosis is 64. This may help to account for the relative historic lack of public health concern about the disease. However, a growing number of patients are being diagnosed in their 30's and 40's. You will recall that I was diagnosed at age 48.

CLL patients eventually have come to learn that while many of us live only three to five years, many others survive for ten years—or measurably longer. It depends on your subset and whether your CLL mutates or not, markers that are only now becoming apparent.

And over time we come to cope with complications such as a suppressed immune system, swollen lymph nodes, weakness, weight loss (myself excluded so far). The most frequent immediate causes of death are bleeding and systemic infections like pneumonia. CLL is truly a devastating disease. Former Secretary of State Larry Eagleburger once said to me "You like wars" as he moved me at the State Department from the Falklands Island War Task Force to run the Office of Israel and Arab-Israel Affairs when Israel was in Lebanon. However, this cancer is a war that I would not have wished on anyone.

Mr. Chairman, I am glad to say that there is now a measure of hope on the research front for CLL patients and their families. The Committee's dedication to funding at adequate levels both NIH and NCI has played a central role in this renewed hope. Everything you do to increase funding for medical research translates directly or indirectly into giving hope to patients in every state and around the world. I say this as someone treated in Europe as well as the U.S.

There is report language going ahead in both the Senate and House strongly encouraging NCI to give full and fair consideration to expanding the scope of research activities through the CLL Research Consortium that I have previously mentioned. But as Senator Specter has said over the years about report language and sense of the Senate resolutions, "druthers do not make dollars". If I had my druthers, I would have Congress earmark $20 million more for the CLL Research Consortium now, but I more or less understand the process. In this case both Congress and NCI with its bypass budget and ability to make decisions internally have to play a role.

This Consortium is a remarkable and long-overdue initiative. It is worthy of more support now, and with the help of doctors, I calculate that it could very usefully expend the $20 million I mentioned previously And use it fruitfully now. NIH and NCI have, of course, long sponsored really productive intramural and extramural re-

search on CLL. But now thanks to NCI a small cadre of researchers in centers ranging from Boston to La Jolla is attempting to discover not only better treatment options but the holy grail of a cure for CLL. I say a small cadre because last week I was privileged to attend a CLL State of the Science meeting at NCI, and a high proportion of the great CLL bench researcher and clinician from the United States and Europe were there. They could all fit in one not-too-large room.

Many of these researchers are going forward under the umbrella of the Consortium itself. It was started last year with an NCI program project grant of $16.5 million to be shared among nine institutions over four years. For that we are grateful, but we can all do the math. That is a humble sum on an annual and institutional basis with which to do lifesaving work. The program project grant is exactly the same amount Mrs. Casey spent to buy the site on Foxhall Road here in Washington for a new residence for our mayors.

To my astonishment, the Consortium is unique. It is a model. It must succeed and is succeeding. Why is it unique? Because for the first time in NCI history it brings together that nation's top researchers on a given type of cancer from different disciplines—genetics, cell biology, immunology and pharmacology, to conduct an integrated program of basic and clinical research. It is also unique in that it brings together many of the great battleships of the cancer wars, ranging from Dana Farber to Johns Hopkins, to M.D. Anderson to Walter Reed. And they are all under the leadership of Dr. Thomas Kipps at the University of California at San Diego. It is not only unique. It is a model in terms of how we might combat other cancers.

The hope is that cross fertilization among leading research institutions which might not otherwise work together will generate life-saving insights, not only about CLL—and this is important—but about many other types of cancers as well. The interaction is already generating new opportunities, opportunities that can not be pursued vigorously at present funding levels. A remarkable CLL Consortium specialist seated near me at last weeks NCI meeting forgot to bring his pen. He told me later that he initially thought he would not need it because he was up on all the latest development. But within the first few minutes of cutting-edge presentations, he had borrowed a pen and went on to scribble all morning. There is much that is new and exciting.

More specifically, more funding is now needed by the Consortium for a stronger research infrastructure, to support further clinical trials on at least six new agents, to fund additional institutional participation, attract additional researchers—particularly in gene therapy, to support expensive data and tissue flow and to encourage the kind of breakthroughs that would attract even more support. The recently developed (and often quite harsh) treatments like Rituxan and Campath are not enough, although desperate patients welcome them. They are not a cure, far from it. They have their costs as well as their benefits. Nevertheless, they show what can be done by NIH, NCI, the CLL Research Consortium and other academic researchers and the pharmaceutical companies.

Simply take as an example the tissue sharing done by the Consortium. Researchers around the country can now secure blood and tissue samples for CLL research purposes. But the process involved in freezing fbrzshipment and-assuring tissue quality at the other end is highly sophisticated and extremely expensive. So is the exchange of data developed by the Consortium. But it is an absolutely vital process.

A measure of success in the model Consortium program is leading the way for other potential collaborative efforts to fight an array of cancers and other diseases that affect the lives of so many of us in this room and millions of other Americans every day. But all this will cost even more money. I believe it is money the American people are willing to spend.

In conclusion, permit me to quote from Dr. Brian Druker, the principal investigator on Gleevec when he was asked how it feels to have made the breakthrough towards a cure for CML. He recently said:

"It's something that is very hard to put into words, and I will share with you what a senior clinical researcher shared with me the other day, and he really put it succinctly. And that was, right now its enjoyable to go to clinic to see our patients being treated with (Gleevec) in a way he never thought imaginable. Patients are grateful in a way we never thought imaginable because of the way they feel and because of the hope that we have restored for the future for them. For me to hear those sorts of words and to know that this is something I have dreamed about for my entire career, this is something I have worked toward, and to actually see it come true is something that I really just can't put into words, but I can tell you, it just feels incredibly good."

Mr. Chairman, if it feels so good to a compassionate doctor like Brian Druker, who once treated me when I fell ill in Portland, Oregon, you can imagine how it

must feel to patients and their families—to know that a cure may be in sight and that for now their lives are being restored to them. Let's make it possible to do the same for CLL and all other blood disorders.

Thank you very much.

STATEMENT OF HAGOP M. KANTARJIAN, M.D., CHAIRMAN, LEUKEMIA DEPARTMENT, M.D. ANDERSON CANCER CENTER

Senator SPECTER. We turn now our final witness on this panel, Dr. Hagop Kantarjian, chairman of the Leukemia Department at M.D. Anderson Cancer Center. He received his B.S. and M.D. from American University of Beirut in Lebanon. Thank you for joining us and we look forward to your testimony.

Dr. KANTARJIAN. Thank you, Senator Specter and Senator Hutchison, for the opportunity to talk about leukemias. I am going to be brief, but I would like to include by written document in the permanent records, if you wish.

Senator SPECTER. The full statement will be made a part of the record, without objection.

Dr. KANTARJIAN. Thank you.

For children and adults, leukemia still presents a major health problem and it affects about 50,000 individuals in the United States every year. Thirty years ago, a diagnosis of leukemia was a death sentence. But today, with the discoveries and the research, we can offer the hope that we will help most of these patients and that we can probably cure over half of these patients.

Aside from the need to cure, treat, and prevent leukemias ultimately, leukemias are an excellent model to study because of the accessibility of the leukemic cells so that a lot of the lessons that we learn from leukemia help other cancers.

How did we improve the cure in leukemia? This was the result of multiple approaches, including chemotherapy, biologic modalities, bone marrow transplantation, and most importantly, the targeted therapies which I will discuss briefly.

But it is important to note that chemotherapy today cures about 80 percent of children with acute lymphocytic leukemia and about 40 to 50 percent of adults with acute leukemia. There are certain acute leukemias which can be treated with only 1 week of chemotherapy, like hairy cell leukemia, or even without chemotherapy but only using vitamin A analogs or arsenic trioxide. Of course, transplant, when it is available, cures about 50 percent of the patients with leukemias and other hematologic cancers.

But as I mentioned, the greatest progress has happened over the past 5 years with the targeted therapies, and in simple terms, leukemias send messages to the outside that identify them as very specific. So, with developed drugs, which are called targeted therapies that look for those signals and there are two kinds which have been very successful: the monoclonal antibodies, which many of them have been approved by the FDA, and then the Gleevec, which is really a magic pill which has no side effects, and based on the research, we think will cure about half of the patients with chronic myeloid leukemia.

M.D. Anderson from the great State of Texas and many other institutions have been involved in this research, and this is made possible only through the granting mechanisms of the NCI and the NIH. The reason is leukemia is a small market for drug companies,

so they do not usually do the research. We have to do it, and when there is a lead, they go for that.

But another important point is we have to have a balanced funding of that research. I personally believe that clinical research has been neglected, and acceleration of the success will come through a balanced funding of both the laboratory and clinical research.

PREPARED STATEMENT

The final question, which I am sure Senator Specter will ask me, so I will ask it to myself, is when will we cure all these leukemias. I truly believe from my heart and also from my mind that based on the base of the discoveries, that we will be able to cure most, if not all, of the leukemias in next 10 years. Thank you.

[The statement follows:]

PREPARED STATEMENT OF HAGOP M. KANTARJIAN

BACKGROUND

Leukemias are categorized by the aggressiveness of their course when untreated (acute versus chronic), and the cell involved (myeloid versus lymphoid). Thus, we often refer to four major types.

Acute		Chronic	
Myeloid	Lymphoid	Myeloid	Lymphoid
acute myeloid leukemia or AML.	acute lymphoid leukemia or ALL.	chronic myeloid leukemia or CML.	chronic lymphoid leukemia or CLL

The overall yearly incidences of leukemias in the USA are:

Leukemia	*Approximate yearly incidence*
AML	8,000
ALL	5,000
CML	7,000
CLL	10,000

Another group related to AML myelodysplastic syndrome (MDS) affects 12,000 to 20,000 individuals/year. Thus leukemias affect overall 40,000–50,000 people in the USA.

CURRENT STATUS AND PROGRESS IN LEUKEMIAS

Over the past 20 years, we have made major progress in the treatment of each of the leukemias. The cure rates in year 2000 for each leukemia and reasons for progress are shown below.

Leukemia	Potential cure (percent)	Average survival	Treatment
Childhood ALL	80	NA	Combination chemotherapy.
Adult ALL	40–50	NA	Same.
Adult AML	20–60	NA	Same.
acute promyelocytic leukemia	70		All trans retinoic acid arsenic trioxide.
CML	50 with transplant	> 7 years	Transplantation Interferon alpha, Gleevec.
CLL		6–8 years	Fludarabine, Rituxan.
-hairy cell leukemia	80	NA	chlorodeoxyadenosine.

NA = Not applicable.

Major areas of treatment discoveries have included:

(1) new chemotherapy drugs

(2) transplant modifications

(3) agents that differentiate leukemias to normal cells such as all-transretinoic acid (vitamin A-like drug) and arsenic trioxide

(4) targeted therapies in the form of:
—monoclonal antibodies: Rituxan, campath 1H, Zevalin, Mylotarg, Bexxar
—small molecules that block signals that stimulate/cause cancer cells: the best example is Gleevec; others include angiogenesis inhibitors, (i.e. agents that block vessels that feed cancers), and others.

WHAT ARE TARGETED THERAPIES

Cancer cells in general, and leukemic cells in particular produce signals or messages which (1) can cause the cancer/leukemia, or (2) identify them selectively (e.g. surface proteins). The past five years have been very exciting in leukemia research because we successfully developed many monoclonal antibodies that target the surface proteins on leukemic cells, and also several "small molecules" that block the signals that may cause leukemias.

Several monoclonal antibodies have now been approved by the FDA for leukemias and are already improving patient prognosis: Rituxan, Campath 1H, Mylotarg. The best example of a "signal inhibitor" is STI571 or Gleevec which blocks the function of protein that causes CML. We believe this very simple small molecule (Gleevec) which is given by mouth, and has almost no side effects (unlike chemotherapy) may lead to the cure of half of all CML patients without requiring transplant. We would like to develop similar selective targeted therapies for most leukemias. Research in these areas is progressing very rapidly. Research in leukemia often cross fertilizes other areas of research in cancer and serves as a useful model to identify new treatments that also help other cancers. Thus funding research in leukemia helps research in other cancer.

FUTURE HOPES, EXPECTATIONS AND NEEDS

Based on the current pace of discoveries, I predict we will be able to cure most leukemias with treatments that have good tolerance in the next 10 years.

To accomplish this, funding by the NIH/NCI is crucial to support:

(1) research projects that investigate new chemotherapy agents, immunologic strategies (e.g. vaccines), targeted therapies, and others.

(2) translational research that translates the laboratory discoveries into clinical research realities.

(3) clinical research, an often neglected area of grant support, without which progress will be inhibited. We need to support clinician-scientists who conduct superior clinical research and make discoveries in human trials that improve the outcome of leukemias.

A BRIEF GLIMPSE AT THE LEUKEMIA PROGRAM AT M.D. ANDERSON CANCER CENTER

Our group at M.D. Anderson includes 15 leukemia specialists who are probably the best in the world. Our leukemia service treats about 2,000 new leukemia cases per year. This is by far the largest program in the world with total dedication to curing one disease—leukemia.

Our cumulative expertise is by far superior to any other program in the world, and we have been responsible for, or associated with most of the discoveries in leukemia therapies. Our program has been funded to a significant extent by the NIH and NCI grant support. Such continued funding mechanisms are vital to the continued success in leukemia research.

Senator SPECTER. That is very encouraging. You are right. I always do ask that question because if you can put something tangible on the line, it impresses Members of the Senate and House.

We have been joined by the senior Republican on the full committee and former chairman. Senator Stevens, would you care to make a statement or question?

STATEMENT OF SENATOR TED STEVENS

Senator STEVENS. I regret I was not here to hear Dr. Klausner. I had fully intended to be here, Doctor, but we are working on the supplemental right now, and I have just dropped by as a fellow cancer survivor, prostate cancer, Mr. Lucchino, to welcome you all and to tell you of our continued support for your endeavors. We hope we can get as much money as possible to meet this medical

research schedule. I am not sure how much money yet there is available, but we will get all there is. Let us put it that way.

Thank you.

Senator SPECTER. I might add that Senator Stevens has been enormously supportive of what this subcommittee has recommended and has vigorously supported the doubling of funding within 5 years for the NIH. So, we thank you.

We are going to have 4-minute rounds by the members.

Let me address the first question to Mr. Pendleton. You comment that you are a sufferer of leukemia without any discernable cure in the offing. How do you feel about a situation where embryos are available which are going to be discarded and these embryos can produce stem cells which have enormous promise for answering and providing a cure for precisely the kind of ailment which you have? How do you feel about that?

Mr. PENDLETON. Senator, you can imagine that I and many and I think perhaps most other patients feel extremely strongly that research must go forward on every front. It is necessary to save the lives of Americans and to make the lives of millions of Americans more bearable.

Senator SPECTER. Mr. Lucchino, the same question. Senator Gordon Smith of Oregon, a very strong pro-life Senator, has made the point that it is very different if you have an embryo in the womb of a woman where there is progress toward the creation of life, contrasted with a discarded embryo in a dish. As someone who has suffered from a variety of forms of cancer, how do you feel about legislation which is now on the books which prevents the National Institutes of Health from using Federal funding to extract stem cells from embryos which might provide a broader range of cures for cancer and other ailments?

Mr. LUCCHINO. Senator, I echo Mr. Pendleton's observations. I readily admit that I am deeply biased on this. I hate these blood diseases so severely that I think that not to avail ourselves of every opportunity is a terrible tragedy.

Senator SPECTER. One of the really critical factors about these hearings is to mobilize public opinion, and if these embryos were to produce life, I would never propose using the stem cells for research. But where they are going to be discarded and you have the positive testimony by the scientists, it seems to me that the point has to be made again and again until it resonates through America.

To Drs. Kantarjian and Horning, brief answers. How important do you think the potential for stem cells are in curing cancer? Ladies first.

Dr. HORNING. Well, as my focus is clinical research, I will speak from that vantage. I would echo what my co-panelists have to say from the patients' perspective and from the physician or clinical researcher perspective. I feel that all leads must be followed. That is going to take many minds and many methods to achieve the cure. As we have heard from Dr. Klausner, there are certain diseases in which the use of embryonic stem cells will be more needed.

Senator SPECTER. With all these embryos available, Dr. Kantarjian, despite that 10-year estimate?

Dr. KANTARJIAN. Right. I think you have put it very clearly. I do not think that stem cell research is debated in the scientific issue. I think it is a political issue because of its potential association to abortions. But from the scientific point of view, stem cell research is very important and discarded embryonic tissue is important for this kind of research.

Senator SPECTER. Thank you very much.

Senator Murray.

Senator MURRAY. Well, thank you very much, Mr. Chairman, and thank you to all of our panelists for excellent testimony. I think it was very clear the bottom line is research, education, and funding, funding, funding. So, I appreciate your message.

I just have one question. I know we have other panelists, so we need to move along. That is the same question I asked to Dr. Klausner earlier. We are debating the Patients' Bill of Rights and one of the contentious issues is whether or not patients should have access to clinical trials. Could either Dr. Kantarjian or Dr. Horning comment on that?

Dr. KANTARJIAN. I think the only way you can make progress is through the clinical trials, and it is a false notion that clinical trials increase the cost. I think clinical trials reduce the cost because they allow accessibility to high quality research that will benefit everybody.

Dr. HORNING. I agree there are data that indicate that the cost of care is not increased by clinical trials and studies show that the quality of care is improved for participants in clinical trials.

Importantly, clinical trials help us to determine the leads that are promising, and when we find the ones that are, we move ahead, and if they are dead ends, then we turn to a different direction. I think the experience of bone marrow transplantation in breast cancer is an excellent example of that.

Senator MURRAY. Thank you very much. Thank you, Mr. Chairman.

Senator SPECTER. Thank you very much, Senator Murray.

Senator Hutchison.

Senator HUTCHISON. Thank you, Mr. Chairman.

Sometimes I think we need a little definition of terms here. For you, we have been throwing around markup of a supplemental, and I wanted to explain to you that the supplemental is the emergency appropriations bill for the needs that we do not have available funds for in the rest of this year for our budget. The markup means we are trying to get the bill out of committee.

Now I want to ask you a question on definition of terms and make sure that we are clear on clinical trials. I want you to define the difference between clinical trials and pure lab research.

Dr. Kantarjian, I want to thank you for being here from M.D. Anderson, which is doing such a wonderful job in cancer research and treatment. I want to ask you to also expand on your point that much of this research needs to be done through NCI and NIH because the pharmaceutical companies cannot focus as much when it is a small number of patients who would use it in the end. I want you to go forward and tell us in the clinical trials, if the NCI and NIH funding is helpful in the clinical trials as much as it could be.

Dr. KANTARJIAN. Let me define a clinical trial. A clinical trial is a controlled investigation where we put forward our best knowledge and we offer it to the patients. So, it is really not what people refer to as experimentation or a guinea pig process. There are no guinea pigs. A clinical trial, or an investigation, offers our best knowledge to the patients. So, it is a two-way benefit where the patients benefit from the most advanced knowledge and we benefit from gathering the data and publishing it. So, clinical trials are very important as opposed to clinical practice, and they are different from laboratory research where you are just looking at the basis mechanisms. You have to translate that knowledge into the clinic. Remember that if you put all your money in the laboratory research, you are not going to cure a single patient and oftentimes the first experience in the first individual will give us a lot of information.

Senator HUTCHISON. Do NCI and NIH do enough to help in the clinical trials? We have been talking about whether insurance should cover it, but are we doing enough in the research area in Government or do we need to make changes there?

Dr. KANTARJIAN. I think we are in the right direction, but there are two areas which need to be improved. One is the process where the insurance companies would pay for the clinical trials, and the second is enough and continuous funding because, as I mentioned, drug companies look for block buster drugs, a billion dollar drug. This does not exist in the leukemias, and this is why the leukemias have been a neglected entity. In fact, most of the discoveries has been made through the funding by the NCI and the FDA and academic institutions and then were taken by the drug companies. So, it is very important to continue that Federal and State funding to the leukemia and hematologic cancer research.

Senator HUTCHISON. Thank you for being here.

Dr. KANTARJIAN. Thank you.

Senator SPECTER. Thank you very much, Senator Hutchison.

Senator Mikulski.

Senator MIKULSKI. Thank you, Mr. Chairman. To all of the witnesses, thank you for your most poignant and instructive testimony.

In the interest of time, I am only going to address one question to Mr. Lucchino. It goes to public education in early detection. In the bill Senator Hutchison and I are working on—and she has been the lead architect—we establish a program at the Centers for Disease Control and Prevention (CDC) and instruct them to create a public awareness program. Also, I think everyone testifying will talk about the need for early detection and screening.

So, let me then get to my question. While we have been strong fighters for women's health, we are often worried that men do not go see doctors. They do not get the early detection and this cuts across all social class lines. My question to you, because you are really, as the Padre guy and the former Orioles guy and Edward Bennett Williams law firm, you have really been with the male culture.

Mr. LUCCHINO. Is that in the nature of a criticism?

Senator MIKULSKI. No. An observation.

My question to you is what advice or insights would you give to really encourage men to go to the doctor and also what could we have the CDC focus on in terms of the kinds of examinations needed or getting men to go in for the early detection? Yours was detected through an annual health exam. Quite frankly, most guys do not go for it.

Mr. LUCCHINO. Right. Well, I consider myself reasonably well informed and well educated, but when I was diagnosed with lymphoma, I had no idea what lymphoma was. At that time, I had no idea what a prostate was. I think there is a crying need for the kind of public awareness that you are talking about.

How to go about it is a multi-faceted question. Certainly events like this hearing today go a long way. I have read more about blood cancers in the last 3 days than I have read in my lifetime. I think that that has a lot to do with Geraldine Ferraro and it has a lot to do with the focus of this committee today. I think that what the baseball world is doing with prostate cancer is an example of what the private sector can and must do. What the Cure for Lymphoma Foundation does is another example of what the private foundation can do. We must talk about it a lot. We must talk about it publicly, privately and certainly with the media. And men need to talk about it as much as possible.

Senator MIKULSKI. Do you think men would be influenced by sports figures and through public service announcements?

Mr. LUCCHINO. I do. I think there is no doubt about that. The cyclist, Lance Armstrong; golfer, Arnold Palmer; hockey player, Mario Lemieux; former Oriole, Eric Davis. I think the experience of these people and the public nature of their experience, talking about it, coming forward, and making the world aware that there is life after a cancer diagnosis is enormously important to the public awareness you are talking about.

Senator MIKULSKI. Well, thank you. Thank you, Mr. Chairman, and to all the panel and to those who, if we had time, ought to be on the panel, the other survivors, thank you.

Senator SPECTER. Thank you very much, Senator Mikulski, and thank you very much.

We will now turn to the next panel. Geraldine Ferraro, Dr. Kenneth Anderson, Dr. John Holaday, and Ms. Kathy Giusti.

We will begin with the Honorable Geraldine Ferraro, who has had an extraordinary career. A lawyer by profession, elected to the House of Representatives in 1978, and then an historical candidacy for the Vice Presidency of the United States with Vice President Mondale in 1984. I join Senator Kay Bailey Hutchison, Congresswoman Ferraro, in praising you for your courage in coming forward.

Ms. FERRARO. Thank you.

Senator SPECTER. It carries a lot of weight when people see someone of your stature who is willing to come forward, and also if it can happen to Geraldine Ferraro, it can happen to anybody. We need all of the public support we can get to push forward the funding and the stem cell research, et cetera. So, thank you for joining us and the floor is yours.

STATEMENT OF GERALDINE FERRARO, FORMER MEMBER OF CONGRESS FROM NEW YORK

Ms. FERRARO. Thank you, Senator, and thank you for having this hearing. I want to thank Senator Harkin and thank you, Senator Hutchison, for helping make it happen, and my two buddies, Senator Mikulski and Senator Murray, for being here. I appreciate it.

I am all too aware of how many things there are to do when you are in session and how little time there is to do them all. So, I am particularly grateful for your allowing us to appear before you to discuss and issue which is, to some of us here, a matter of life and death.

Several months ago I was at home watching the news and saw our former colleague, Joe Moakley, at his press conference disclosing that he had been diagnosed with a blood cancer, leukemia, which is neither curable nor treatable and announcing that he would not seek reelection. My heart went out to him in part because he was such a terrific person who really loved the Congress, and his announcement was so terribly final. But also because I knew what he was going through emotionally dealing with this disease. In December of 1998, I too was diagnosed with a blood cancer, multiple myeloma, which is also not curable. Let me hasten to add, however, that unlike Joe's situation, at least for the present, my cancer is treatable.

I have chosen not to be public about my health until now. That is one of the benefits of losing an election.

You can keep your private life private. But I am here because I want to make sure that the public got to know about multiple myeloma and I wanted to point out to you just how important research dollars are to dealing with this disease.

Let me start by saying I am a very lucky woman. First of all, I have the best doctors caring for me. It is because of one of those doctors, Ronald MacKenzie, my internist, that I was diagnosed very early. I had gone for my annual checkup and he noticed in looking over my blood test results that my white blood count was slightly elevated. He went back and checked my previous years' records and saw that there was a steady but slow progression upward of the white cell count over the years. He called me and said he wanted to see me and that he was sending my blood out for additional tests because it seemed that I had either leukemia, lymphoma, or multiple myeloma.

I must say I was a bit taken aback. I did not even know what multiple myeloma was. I had never heard of it. Dr. MacKenzie explained that it was a blood cancer that attacks the bones. Most people do not find out that they have it until a symptom appears that needs explanation, like aching or broken bones. And I had no symptoms.

My initial reaction was thank God it is me and not one of my children. As much as we want to believe that we are indispensable to our families, my children are all grown and quite independent. But they are also married and they have little children of their own who most definitely do need them.

My second reaction was: Why cancer? That is not a disease that is in my family. We are big on strokes and heart attacks.

Even my mother who smoked died of emphysema, not lung cancer. So, how did I get multiple myeloma? Was it the environment? Was it stress? And we all know I have had a little of that over the years. Was there some hidden genetic disposition to the disease, and if so, can we check my children and grandchildren to be sure I have not passed that cancer gene on to them? And going beyond me, what is it that make African Americans almost two and a half times more likely than Caucasians to come down with this disease? Why is it that multiple myeloma historically manifests itself in people who are older? Hopefully, future research will be able to answer all of those questions.

When we left Dr. MacKenzie that day, we were feeling pretty down. But the holidays were fast approaching, and after seeing John's devastation on hearing the news, I just did not have the heart to tell my kids until after Christmas. But once the holidays were behind us, we told them, and then we went to see my second wonderful doctor, Jeffrey Teppler, who is an oncologist.

Before I go on, I want to point out that I keep using the term "we." That is not the royal "we." That is my husband John Zaccaro and me. We have been best friends since college. Next month we will be married for 41 years. We totally enjoy each other's company but professionally we have led rather independent lives. Since my diagnosis, however, John drops everything at the office to drive me to the doctor, to sit with me for 2 hours at the hospital when I am getting an infusion, to fly to Boston to meet with my third wonderful doctor, Ken Anderson, from whom you will hear shortly. And as a matter of fact, my husband is here today with my eldest daughter Donna.

But back to Dr. Teppler. When I was first diagnosed, my cancer was inactive. No protein showed in my blood, none in my urine. So, Dr. Teppler took rather frequent bone marrow samples and did blood and urine tests on a monthly basis. And I started monthly infusions of a bone-strengthening drug called pamidronate.

In June of last year, he called me and told me that the cancer had become active and that he had spoken with Dr. Anderson, whom I had met shortly after diagnosis, and they agreed that I should start taking steroids.

Now, I thought I was going to be able to hit the golf ball further, swim faster, run like the wind once I got on steroids.

Unfortunately, this type of steroid has none of the beneficial effects that the steroids that athletes take. It did deal with the cancer, though it was mood altering and made me terribly irritable. It also made me slightly puffy which was not all that bad since all of my wrinkles temporarily disappeared without the cost or inconvenience of a face lift.

I continued taking the steroids through the summer and early fall and they worked beautifully, reducing the cancer protein, until November. And then I plateaued. It was time to go to Dr. Anderson to discuss stem cell transplants.

Though I was not happy about it, I was resigned to the fact that I would need the procedure since I had been told it was my next step in treating the disease. And without treatment, quite simply I will die. I was told the stem cell transplant would involve 3 weeks in the hospital, that I would be getting massive doses of chemo-

therapy, followed by radiation, that my immune system would be totally destroyed and that I would need approximately 3 months at home to recuperate.

I was worried about how I would deal with that amount of time out of circulation. I worried about my business, my family, and to be quite frank, I worried about myself.

The one thing I was not worried about was the cost. I am told the price tag for the procedure is $50,000 to $100,000. I am now eligible for Medicare and Medicare covers the procedure. But even if it did not, my insurance does, and if my insurance did not cover it, I could still afford to pay for the procedure myself if I need it. But what about those who cannot? What about those who do not have health care coverage? I guess those are two questions that will properly be answered at a future hearing on health care legislation instead of here today.

Dr. Anderson went through the whole process with John, my youngest daughter Laura, and me. And then he said that several of his patients had opted to take thalidomide as an alternative to having the stem cell procedure done. I was intrigued. I was having babies in the 1960's when thalidomide was making headlines as a dreaded pill that, when taken by pregnant women, caused severe damage to fetuses. Children were being born with all kinds of deformities. But what destroyed healthy growth then was now being used to prevent cancer growth. Dr. Anderson described for us just how thalidomide works, which I am sure he will do for you, and when we heard that it had the potential for treating the disease with minimal side effects, that if it did not work, we were not precluded from doing the stem cell transplant in the future, we opted to try thalidomide.

I have been taking thalidomide since November. It is working. Once a month, I still go for an infusion, and once a month I get blood and urine tests. Then I wait for three very long days until my test comes back to hear from Dr. Teppler. Am I still doing well? Have the cancer cells figured out a way to fight the thalidomide? And if they have, what if any option do I have before I deal with a stem cell transplant?

I do not expect you to answer those questions, Senators. Those I reserve for Dr. Anderson. And I have such confidence in him and the other researchers who are dealing with multiple myeloma that I know they will have the next step ready for me when I need to take it.

But they need you and your colleagues in the Congress to help. They need more awareness and attention being paid to blood cancers so that people will test early and be diagnosed earlier. They need research dollars to continue to search for new treatments and a cure, and they need faster approval by the FDA of new drugs.

Pharmaceutical companies have been slow to underwrite research for multiple myeloma because each different blood cancer requires different treatment. What is good for leukemia or lymphoma will not help me. So, if you take each of the blood cancers separately, we are talking about orphan drugs since there just are not enough potential users of each to make it financially worthwhile for the pharmaceutical companies.

On the other hand, this is still a huge problem for this country, for if we lump together leukemia, lymphoma, and multiple myeloma, last year's figures show that the mortality rate for blood cancers is second only to lung cancer, 20 percent higher than colon blood, one-third higher than breast cancer, and almost twice as high as prostate cancer. Those diseases receive far more attention and far more funding.

Now I am not suggesting for 1 minute that attention or funding to the other diseases be reduced. My husband is a survivor of colon cancer because of early detection. I nagged my two older children until they got a colonoscopy, and I will get up on a soapbox and tell the world how important it is to be tested to detect that disease because it is curable. I also served when I was in the House and even after on a breast cancer task force, and I have spoken out and walked more than once to raise money for that cause which I will continue to do. But what I am suggesting is that blood cancers are a serious and costly health concern and they too need our attention and funding.

Multiple myeloma is hitting a lot of elderly, and though I wince when I refer to myself that way, I am not an unusual candidate for this disease. But just think about the consequence of that demographic. I mentioned before that if I need a stem cell transplant, it will cost between $50,000 and $100,000 and that Medicare will pay for it. Instead, my insurance company is paying $264 a month for a prescription of thalidomide. A year ago, that cheaper option of thalidomide was not available. Research made the difference. Now, what happens when thalidomide stops working, and I go month to month not knowing when Dr. Teppler will call and tell me that? Will Dr. Anderson be able to give me some new drug, or will he have to tell me that it is in clinicals and he is not quite sure when it will be approved, so it is time for a transplant? It almost goes without saying that combining investment and research with faster Government approval of drugs is a cost effective way of dealing with the expense of this disease to our health care system.

I told you when I started that I am a lucky woman. I have great doctors, an early diagnosis, and up-to-the-minute treatment that works. But cancer does not only eat at your body. It is a disease that can destroy you both emotionally and psychologically. I am blessed with a family that is always there to boost me up. In addition to their constant concern for me, my daughter Donna has taken her business and media experience and put it to work to help the Multiple Myeloma Research Foundation raise awareness and money. My son John, who is a lawyer, has filled in and taken over the headaches of John's business so his dad can be with me. Laura is the doctor who keeps an eye on my test results and asks the questions I forget to ask and answers the ones that I am too embarrassed to ask. My four grandbabies give me hugs and kisses and a thousands reasons a day I want to fight this thing. They and John, of course, and a few close friends—and Barbara Mikulski was one of the people I confided in almost immediately after I found out that I had this—have given me the emotional support that all of us need when we are slapped in the face with our mortality. Living in New York City, I am never quite sure when I run

into a street to hail a cab that I am going to live long enough to ride in it.

But hearing that you have a disease that is incurable with an average life span of just 3 years does make one stop and notice.

I expect that with my trio of medical miracle workers, with the love of my family and friends, with my mother and all the nuns who took care of me a as little girl praying for me, that I will be around at least until 2010 so that I can take advantage of President Bush's elimination of the inheritance tax—hopefully even after that so that I can be invited to the inauguration of the first female President of the United States, Senators.

PREPARED STATEMENT

In the meantime, however, I, as well as every other multiple myeloma patient, am hoping that you, Senators, will provide help to these doctors so they can continue their research and eventually find a cure to this disease.

Again, thank you, Mr. Chairman, Senator Specter, Senator Hutchison, Senator Murray, Senator Mikulski.

[The statement follows:]

PREPARED STATEMENT OF GERALDINE A. FERRARO

I want to begin by thanking you, Mr. Chairman, and Senator Spector for holding this hearing and Senator Hutchinson for helping to make it happen. As a former member, I am all too aware of how many things there are to do when you are in session and how little time there is to do them all, so I am particularly grateful for your allowing us to appear before you to discuss an issue which is, to some of us here, a matter of life and death.

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Again, thank you, Mr. Chairman and Senator Spector for holding this hearing.

Senator SPECTER. Thank you very much. We very much appreciate your coming forward and the quality of your testimony. We are pleased that you used this occasion to announce your candidacy for the presidency.

Some may have noticed that the red light was on a little longer than usual. The prerogative of the chair is to allow that when you have ex-vice presidential candidates who are women.

Ms. FERRARO. I appreciate that, Senator. Thank you.

Senator SPECTER. I am going to waive my 4 minutes to make up for most of the extra time.

Senator Murray has a commitment and wanted to make just one brief comment before excusing herself. Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman, for accommodating me.

Ms. Ferraro, I just want to thank you. You have been a role model for so many women who are in politics, I being one of them. Watching you run for Vice President was an inspiration to many of us, and I know to many, many young women in this country still today who now see politics as something they can do. I would not be sitting on this committee in this place without people like you who paved the way.

You are doing it again with your courage and your humor, enlightening all of us about how we need to take on another little issue, blood cancers. And I just want to thank you so much for all you have done for so many of us. Thank you very much.

Senator SPECTER. Thank you, Senator Murray.

STATEMENT OF KATHRYN E. GIUSTI, PRESIDENT, MULTIPLE MYELOMA RESEARCH FOUNDATION

Senator SPECTER. We now turn to Ms. Kathy Giusti, who founded the Multiple Myeloma Research Foundation in 1996 after being diagnosed with the ailment. She brings 16 years of experience as a pharmaceutical executive to her role as President of the foundation. Thank you for joining us, and we look forward to your testimony.

Ms. GIUSTI. Thank you so much, Mr. Chairman and Senator Hutchison.

My name is Kathy Giusti. I am a multiple myeloma patient, and I am also president of the Multiple Myeloma Research Foundation. I just want to thank you for your support of blood cancers.

I was, indeed, diagnosed with myeloma in 1996 at the time I was 37, a wife, the mother of a 1-year-old little girl named Nicole, and I was also in the height of my career as the highest ranked woman executive at G.D. Searle Pharmaceuticals in Chicago.

When I was diagnosed, I heard the same statistics that Geraldine did. I heard that multiple myeloma has no cure, and I heard on average multiple myeloma patients live about 3 years. So, of course, I transferred that into my own life, and what I realized was I would die before my 40th birthday and I would die before I ever saw my little girl go to kindergarten.

I really could not believe then that a cancer existed that had absolutely no cure, but I can tell you that my experience in the pharmaceutical industry helped me to understand why. With 14,000 patients diagnosed with myeloma each year, it is really hard to make

myeloma a top priority by pharmaceutical companies. When you compare the return on investment for myeloma with other cancers such as breast cancer or prostate cancer, it does not compare. So, when I kept searching every annual report looking for a new drug in the pipeline in 1996, I was pretty devastated.

I think for me one statistic said it all. Basically it was the fact that 28 percent of myeloma patients will be alive 5 years after they are diagnosed, and I compared that to the 90 percent survival that we now see with breast cancer and prostate cancer. So, it was obvious. Multiple myeloma has been neglected for decades.

So, I resigned from my career in the pharmaceutical industry and dedicated my time to trying to raise money for multiple myeloma research. I founded the foundation with my twin sister, Karen Andrews, who is an attorney, and basically what our foundation does is we serve as a venture capital company raising money for early myeloma research, making sure we validate the best ideas and then we turn them over to the pharmaceutical companies and the NCI to move them forward.

In 3 short years, we have raised over $10 million. We have funded over $8 million in myeloma research grants. Over 75 percent of the grants we fund have been published or presented. I think the true results of what we have done, stem cell transplants are now safer, patients are enrolling in new vaccine trials, and we are helping to pay to understand why thalidomide is working for patients like Geraldine Ferraro.

The MMRF is just one of several private foundations funding myeloma research. I am joined here today by the International Myeloma Foundation, by the Leukemia Society, the McCarty Foundation, and together we will fund between $10 million and $15 million in myeloma research. The NCI will fund about $18 million. So, you are seeing one of the highest ratios of private to public sector funding in oncology.

Now I can tell you that Geraldine Ferraro and I are not your typical multiple myeloma patients. We both sit here before you looking perfectly healthy and living as active lives as we can. But running the foundation, my job is to talk to hundreds of patients every month who are dying, who are facing excruciating pain, severe anemia, and who are living very difficult lives.

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So, I urge you to work with us to make sure that the PRG priorities are implemented. I know that I will dedicate whatever time Dr. Klausner needs me to to turn those PRG priorities into a good business plan, and I know Geraldine and her daughter Donna will help me as well. So, I ask you to be part of our team and help move the progress forward.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF KATHRYN E. GIUSTI

Mr. Chairman, my name is Kathy Giusti. I am a multiple myeloma patient and President of the Multiple Myeloma Research Foundation (MMRF). I am pleased to appear here today and thank you and the Committee for your commitment to the issues that surround blood cancers.

I was diagnosed with multiple myeloma in 1996. I was 37, a wife, the mother of a one year old little girl. I was also at the height of my career in the pharmaceutical industry-the most senior female executive at G.D. Searle in Chicago.

I heard the same statistics that Congresswoman Ferraro did. Multiple myeloma has no cure. Multiple myeloma patients live on average, three years. I quickly put the doctor's words in real terms. I would die before my 40th birthday. I would die before seeing my little girl go to kindergarten.

I could not believe a cancer existed that had absolutely no cure, but my experience in industry helped me understand why. With 14,000 Americans diagnosed with multiple myeloma each year, multiple myeloma could not be a priority for the pharmaceutical industry. The return on investment for myeloma could never compare with the return on more prevalent forms of cancer such as breast and prostate cancer. I read every pharmaceutical journal searching for new compounds in the pipeline for myeloma. I found none. I contacted the National Cancer Institute (NCI). But with so little awareness, the NCI was investing just 12 million dollars in myeloma that year.

One statistic said it all . . . only 28 percent of myeloma patients would be alive five years after diagnosis compared with the 90 percent five-year survival seen in breast and prostate cancer and the 62 percent survival for all cancers combined.

It seemed clear to me that myeloma had been neglected for decades. In 1997, I resigned from my career in the pharmaceutical industry and with my twin sister Karen Andrews, an attorney, founded the MMRF with one goal in mind-to fund research. We knew the MMRF could act as a venture capital firm by funding early myeloma research and validating new ideas. The pharmaceutical industry and NCI could then take the most promising ideas and move them forward. In three short years, we've made tremendous progress. The MMRF has raised over ten million dollars. We have committed eight million dollars to research grants and research grants with the remaining funds supporting education. Over 75 percent of the grants we have funded have been published or presented at major medical meetings.

The result of our efforts? Stem cell transplants are safer and more effective than ever before. New vaccine trials are enrolling patients. We are learning why thalidomide and proteasome inhibitors are working. Our patient and physician outreach is expediting clinical trials.

The MMRF is one of several groups in the private sector raising funds for myeloma research. Together with the Leukemia and Lymphoma Society, the McCarty Foundation, and the International Myeloma Foundation, we will fund ten million dollars in myeloma research this year alone. The NCI will distribute approximately $18 million in funds. This is one of the highest ratios of private to public support seen in the cancer field.

How can you help us keep this momentum going? How can you help the 700,000 patients suffering with blood cancers today? You can make the Progress Review Group priorities a reality. Right now, we have a list of priorities that will reduce the time it takes to bring new compounds to market from the current 7.2 years to the 2 years we saw with Gleevec. That list must now be developed and quantified in terms of manpower, time and funding. We need a clear action plan by year-end.

Why do we have this sense of urgency? Because this year alone, 60,000 Americans will die from blood cancers, second only to lung cancer. We have promising compounds in the clinic. We need to get them to the bedside . . . quickly.

I am one of the lucky ones. I have lived five years with myeloma. In those years, I have celebrated my 40th birthday, watched my daughter Nicole start kindergarten and first grade and was blessed with a son named David. But I am not a typical myeloma patient. The many friends I have met through this illness I have also lost. The many funerals I attend are a constant reminder that while we have come so far . . . we are not yet there. I urge you to help us implement the PRG priorities quickly. Your efforts will bring new treatments to Congresswoman Ferraro and the hundreds of patients you see here today. And when the inevitable day comes for my husband and me to tell our young children mommy has cancer, we can also tell them it's ok, mom has a fighting chance. Thank you.

Senator SPECTER. Thank you very much for your testimony, Ms. Giusti.

STATEMENT OF KENNETH C. ANDERSON, M.D., PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL

Senator SPECTER. We turn now to Dr. Kenneth Anderson, Professor of Medicine at Harvard Medical School and Medical Director of the Kraft Family Donor Center. He is a member of the Depart-

ment of Adult Oncology at Dana-Farber Cancer Institute. Thank you for joining us, Dr. Anderson, and we look forward to your testimony.

Dr. ANDERSON. Thank you very much. It is a pleasure to be here and I thank you all for your consideration and support of the blood cancers, illustrated here for us today.

As was said, I am a professor of medicine at Dana-Farber Cancer Institute and also a Doris Duke Distinguished Clinical Research Scientist, which means plainly I am committed to developing new treatments in the laboratory to get to the bedside for blood cancers.

I focus in particular on multiple myeloma. It is 1 percent of all cancers. It accounts for 2 percent of all cancer deaths. Some 14,000 new Americans get it every year, 50,000 total are affected, and 11,200 individuals died last year of myeloma.

What does it do? Myeloma is the accumulation of these abnormal tumor plasma cells in the bone marrow. Patients get infections, bleeding, and they get fractures of their bones because of thinning of the bone, which precludes just simple activities of daily life. They also get high blood calciums, renal failure, and devastating nerve damage.

What can we do about it? We can treat it with conventional therapy to extend the average survival to 3 to 4 years. High dose therapy and stem cell transplant can modestly improve that, perhaps to 4 to 5 years. Unfortunately and tragically, we cannot cure it.

There is very great reason for promise and optimism. You have already heard of the novel use of thalidomide to treat myeloma. The novel concept is it not only kills the tumor cell directly, but it acts in the bone marrow neighborhood in a way to make it impossible for the myeloma cell to grow and live there. You have heard beautiful testimony earlier this morning about Gleevec, which specifically is a targeted drug to inhibit the protein that causes chronic myelocytic leukemia. I call these designer drugs, and in myeloma we have such drugs coming that will either blow the fuse on the growth circuit or turn on the death circuit in myeloma cells.

Finally, there is that strategy based on vaccines which will stimulate the patient's own immune system to reject myeloma, just like the natural immunity clears an infection.

You heard nicely from Dr. Klausner earlier about the Progress Review Group process in blood cancers that has recently concluded. One important priority that was identified was, in fact, an initiative, a collaboration between academia, Government, industry, and patients, to shorten the time, which is now 5 to 10 years, down to 2 years that it takes to get a novel compound into general clinical practice.

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I know that you have all been inspired, as have I, this morning by the courage that has been demonstrated in the face of incredible adversity by Geraldine Ferraro, by Kathy Giusti, by Alan Bailey, and by so many other patients who are in this room who have currently incurable diseases. The Progress Review Group process has laid out a road map for us to make a difference in the next 5 years. If we fail to do that, we will be condemning patients with blood

cancers to needless pain, suffering, and premature death. In contrast, if you partner with us, we are now poised to make a huge difference in prolonging the overall survival and quality of life for patients with blood cancers worldwide.

[The statement follows:]

PREPARED STATEMENT OF KENNETH C. ANDERSON

Good morning. I am Ken Anderson, M.D., a Professor of Medicine at Harvard Medical School and Dana-Farber Cancer Institute in Boston, and I thank you most sincerely for the chance to speak here today. I am also pleased to be here as a Doris Duke Distinguished Clinical Research Scientist; a member of the Boards of Directors and Scientific Advisors of the Multiple Myeloma Research Foundation and the International Myeloma Foundation; as chairman of the National Comprehensive Cancer Center Network Myeloma Guidelines Panel; as a member of the Medical and Scientific Committee of the Leukemia & Lymphoma Society of America, and as a member of National Cancer Institute Scientific Review Group D, Subcommittee D, for Clinical Research Studies. I was also honored and privileged to serve as a Co Chairperson of the recent Lymphoma, Leukemia, and Myeloma Progress Review Group (LLMPRG), which was a multidisciplinary panel of prominent scientists, clinicians, advocates, and industry representatives convened by the National Cancer Institute to prioritize the national research agenda for blood cancers. In the past the blood cancers have represented a model for the treatment of cancer with chemotherapy. Specifically, chemotherapy was pioneered 50 years ago in childhood acute lymphoblastic leukemia, and increasing the dose and combining drugs has led to cure in the majority of cases. Use of high doses of chemotherapy followed by bone marrow or blood stem cell transplantation was also pioneered in blood cancers, and is curative in some patients with leukemia. Most excitingly, the recently approval of Glivec represents the first example of a designer drug which specifically targets the abnormal protein that causes chronic myelocytic leukemia. Such specifically targeted drugs represent a new treatment paradigm with great promise for improving the outcome of patients with cancer generally, as well as those with other illnesses such as HIV infection. Therefore implementation of the initiatives proposed by the recent LLMPRG will have broad and important implications for improved medical practice.

My specific basic science and clinical interests focus on multiple myeloma. Multiple myeloma is the second most common blood cancer, representing 1 percent of all cancers and accounting for 2 percent of cancer deaths. There were 14,400 new cases, 50,000 total patients affected, and 11,200 deaths from myeloma in the United States in 2000. Myeloma is the fourth fastest growing cancer in terms of mortality, and importantly, is in the top 10 causes of death among African Americans. Although traditionally considered as a disease of the elderly, the average age of affected individuals is approximately 60 years. With the aging of the U.S. population, its incidence is expected to further increase. Myeloma, a bone marrow cancer like leukemia, is characterized by the excess accumulation of antibody forming (plasma) cells in the bone marrow, in association with the abnormal antibody (monoclonal protein) made by these plasma cells accumulating in patients' blood and/or urine. Affected patients develop anemia or low red blood cells with fatigue, low white blood cells with related increased risk of infection, and low platelet count with related risk of bleeding. The most debilitating feature of myeloma is thinning of bone (osteoporosis) or holes in bone (lytic lesions), with related fractures, pain, and major limitations in quality of life and activities of normal daily living. Other less frequent complications include kidney failure, high blood calcium, and nerve damage. Conventional chemotherapy prolongs survival to a median of 3 to 4 years, and high dose therapy followed by a blood stem cell transplant can modestly extend median survival to 4 to 5 years. Tragically, few, if any, patients are cured. Treatment of myeloma-related complications can improve quality of life for patients and includes transfusions or growth factors to treat patients with low red blood cell, white blood cell, or platelet counts. Importantly, the use of bisphosphonates can slow the development of bone-related complications, decrease related pain, and thereby improve the quality of life of patients with myeloma.

Although conventional and high dose therapy extends survival, disease almost always recurs and becomes resistant to all known treatments. As a result few, if any, patients have been cured to date. Importantly, however, major progress in our understanding of the biology of myeloma has occurred in the past two years, providing the framework for novel very promising therapies. The first major novel concept is the use of drugs which not only target and kill the myeloma cells directly, but also

target their bone marrow environment to inhibit the localization of myeloma cells in marrow, to abrogate the production of factors in marrow which promote the growth and survival of myeloma cells, and to block new blood vessel formation or "angiogenesis". Excitingly some of these new drugs also augment a patient's own immune system to recognize and kill his own myeloma cells, much as an infection can be cleared by our natural immune response. Examples of these drugs include thalidomide and its potentimmunomodulatory (IMiD) analogs, as well as proteasome inhibitors. Even in patients whose myeloma has recurred despite all conventional and high dose therapies, thalidomide achieves significant responses and prolongs survival of 30 percent patients, demonstrating that these new drugs can overcome resistance that myeloma cells have developed to conventional therapies. Once these drugs are tested and found to be safe and effective in patients with advanced disease, they are rapidly evaluated as treatment for newly diagnosed patients. Excitingly, early clinical trials suggest that treatment with these new biologically based therapies can have an even greater impact (80 percent responses) when used as the initial therapy for myeloma. Major laboratory research is currently ongoing to specifically identify the targets of these new drugs in both myeioma cells and the bone marrow in order to develop even better drugs, more selective against tumor cells, which are both more efficacious and have fewer side effects. For example, the revolution in our understanding of the human genome allows for characterization of the temporal sequence of changes in expression of up to 20,000 genes which are either upregulated or decreased in response to drug treatment, markedly enhancing our ability to define mechansims of drug anti-myeloma activity on the one hand, versus mechanisms whereby tumor cells escape or resist therapy on the other.

In addition to these novel drugs targeting not only the tumor cells, but also its interaction with the bone marrow neighborhood, two other novel treatment approaches offer great promise. The first is based upon basic scientific studies which can delineate those circuits inside myeloma cells which mediate their unregulated growth, as well as those molecular circuits which allow them to resist normal death processes. Definition of these pathways has allowed for the development of "circuit breakers", novel drugs which specifically interrupt tumor cell growth; or "circuit makers", which specifically turn on death signals inside myeloma cells. The promise of this approach is best illustrated by Glivec, the novel drug which specifically inhibits the abnormal protein which causes chronic myelocytic leukemia. It has already markedly improved outcome for patients with this illness, and has recently received FDA approval.

A third major area of promise for the treatment of blood cancers, in particular multiple myeloma, are the immune-based therapies. These can consist of specialized transfusions of the patient's own or a sibling's cells which are programmed to recognize and kill patient myeloma cells. Immune therapies also include vaccines against the patient's tumor cell or fingerprint proteins on the tumor cell surface. The goal here is to stimulate the patient's immune system to recognize and reject their own tumor cells, just as natural immunity readily clears an infection. An important advantage of these approaches is their high selectivity and efficiency in targeting and killing tumor cells, thereby avoiding the side effects attendant to current conventional therapies which are non-selective and kill normal, as well as tumor, cells.

Once novel therapies such as these are identified to be of potential benefit to patients in laboratory preclinical studies, there is an urgent need for rapidly moving these agents from the bench (laboratory) to the bedside (clinic), where their clinical utility can be assessed in treatment protocols. The need is particularly immediate for patients with myeloma, for whom no curative therapy currently exists. As I mentioned at the outset, a panel of prominent scientists, clinicians, advocates, and industry representatives was convened by the National Cancer Institute and identified research priorities in blood cancers. Most importantly, the LLMPRG has proposed a new initiative—The Cancer Translational Research Allied Consortium (C–TRAC). C–TRAC represents a unique opportunity to shorten drug development time in the United States from the current 5–10 years to 2 years through a novel alliance among academia, industry, government, and patients, and holds great promise to get novel targeted therapies to our patients with blood cancers who so desperately need them.

In summary, basic science advances now offer an unprecendented opportunity to solve the mysteries of the past and specifically and effectively treat blood cancers. The roadmap to achieve this goal has been laid out by the LLMPRG process of the National Cancer Institute. I am sure that you are both personally moved and inspired by the extraordinary courage in the face of personal adversity exemplified here today by Geraldine Ferraro, Kathy Giusti, and the numerous other patients here today. As a basic science and clinical researcher and caregiver, I extend my heartfelt and genuine admiration and thanks for your consideration and support for

these research initiatives which will markedly enhance the survival and quality of life of affected patients worldwide.

Senator SPECTER. What do you think you can do within 5 years, Dr. Anderson?

Dr. ANDERSON. I think that within 5 years there will be many more of the leukemias which are cured. I think that if myeloma may not be cured, certainly it will be turned into a chronic illness not unlike hypertension or other illnesses with which patients can grow old gracefully, as I like to say.

Senator SPECTER. Thank you very much, Dr. Anderson.

I have presided at a lot of hearings. I have never heard so much applause.

STATEMENT OF JOHN W. HOLADAY, Ph.D., CHAIRMAN AND CEO, ENTREMED, INC.

Senator SPECTER. Dr. John Holaday, Chairman and CEO and Cofounder of EntreMed, Inc., a biotech company in Rockville, MD. He served as Chief Biochemist at the Division of Neuropsychiatry at Walter Reed Hospital. We very much appreciate your being here, Dr. Holaday, and look forward to your testimony.

Dr. HOLADAY. It is my pleasure. I thank you, Senator Specter, also Senator Hutchison, and my favorite Senator, Senator Mikulski, who represents the great State of Maryland where Rockville and certainly EntreMed are located.

It is my pleasure to tell you today that there is some good news on the horizon. I want to share with you a story that is part of our common passion at EntreMed and shared by many researchers throughout the world that a new field of medicine that has evolved around understanding the growth of new blood vessels in various diseases like cancer might have great promise in the treatment of multiple myeloma and various other forms of blood cancers.

Specifically over 30 years ago, Dr. Judah Folkman, when working at the Navy, realized that it is impossible for tumors to grow, whether they are solid tumors or blood tumors, without the proliferation of new blood vessels to feed that growth. Now, in retrospect, that seems to be a rather intuitive thought, but it has taken quite some time for that to be recognized as a potential forefront in the field of medicine.

Subsequent to his years of effort, a young man by the name of Dr. Robert D'Amato realized that the drug thalidomide, which was known to cause the birth defects in the early 1960's, very likely caused these defects by blocking the growth of blood vessels, and thus the normal limb formation could not occur. So, with this great step of realization, Dr. D'Amato said maybe thalidomide is an antiangiogenic drug that could inhibit the growth of blood vessels and thus have efficacy in the treatment of a variety of forms of cancer. Indeed, teaming up with Dr. D'Amato, who first published this with Dr. Folkman in the proceedings of the National Academy of Sciences in 1994, we at EntreMed, along with the National Cancer Institute and Dr. Klausner's team, proceeded rapidly toward phase II studies to demonstrate that thalidomide has effects on a number of different forms of cancer.

It was Dr. Folkman who actually recognized the potential of its use in multiple myeloma who recommended to another pioneer in

this field, Dr. Barlogi, that he try thalidomide for the treatment of that particular cancer patient. And subsequently other leaders, such as Dr. Anderson, are continuing in this quest to find new ways of using this old drug for a good and a new purpose.

When we were developing this molecule, we found it was tough to get big pharmaceutical companies, unlike us small ones, to buy into the concept that you could resurrect a drug with this terrible heritage. We succeeded in finding a relationship with Celgene which was a small company like us, but they had the opportunity to distribute thalidomide, and through that relationship, we have been at EntreMed able to have this drug on the market for the last 3 years, or at least available to patients, with the leadership of such people as Dr. Anderson and with the great hope that is provided to people like Geraldine Ferraro. We are pleased to have had this opportunity.

I want to also say that we are on the cusp of many new developments in this field. It is not true that all of the research comes from Government laboratories. We in the biotech industry represent a very committed and dedicated group of people whose passion it is to make a difference in the lives of patients. In that context, we have a new series of molecules that will come along as next generation relatives of thalidomide, and another drug called Panzem, or 2-methoxyestradiol, a natural substance where we have phase II studies presently underway at the Mayo Clinic in patients with multiple myeloma and shortly to begin with Dr. Anderson at the Dana-Farber.

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So, again, there is reason for hope. We encourage patients as always to be very proactive in the management of their disease and to consider, as they look forward, the opportunities that this new field of medicine, inhibition of angiogenesis, pioneered by Dr. Folkman so many years ago, might have as a new way of looking at diseases and particularly diseases of the blood.

I thank you.

[The statement follows:]

PREPARED STATEMENT OF JOHN W. HOLADAY

Chairman Harkin, members of the Committee, I wish to thank you for your kindness in allowing me the opportunity to testify before the Committee today.

My name is Dr. John Holaday. I am the founder, Chairman and CEO of EntreMed, Inc. a biotechnology company located in Rockville, Maryland, just outside the Beltway. I formed EntreMed in 1991 to bring entrepreneurship to medicine. In doing so, EntreMed has assumed the risk of revolutionizing drug discovery and development for the benefit of patients. We now employ 120. exceptional scientists and staff, all sharing a common passion to bring new drugs to cancer patients—including those with solid tumors and blood cancers—in the hope of providing them with a more livable life, and allowing them to live with their disease, not die from it.

I would like to inform the Committee of one cancer breakthrough that has dramatically changed thinking about how to conquer this horrible disease and the role EntreMed plays in bringing these new weapons to the fight against cancer. Over thirty years ago, Dr. Judah Folkman, while working as a Naval Officer at Naval Medical Research Institute in Bethesda, Maryland, discovered an ingenious method to stopping tumor growth. He demonstrated that cancerous tumors require the simultaneous growth of blood vessels to feed their malignant cells. In doing so, he pioneered the field of medicine called "angiogenesis."

His quest to challenge conventional thinking in the entrenched practice of oncology has been long and arduous, but fortunately it is now beginning to pay off for

cancer patients. Dr. Folkman's research at Children's Hospital, an affiliate of Harvard Medical School in Boston, has produced revolutionary molecules, such as Thalidomide, Endostatin, Angiostatin and Panzem, that are shown to arrest cancer growth in mice by starving tumors of their blood supply. EntreMed took these promising molecules from the laboratory to the cancer clinic in record time, in collaboration with Dr. Folkman, Children's Hospital and the National Cancer Institute.

But this story goes back even further, and with the Committee's indulgence, I will take a moment to explain it. Over twenty years ago, Robert D'Amato was finishing high school when he won the International Science Fair for his discovery of a new way to detect multiple sclerosis by measuring changes in vision. His prize provided him with the opportunity to work in my laboratories at the Walter Reed Army Institute of Research for a summer. While there, he learned the basics of academic medical research and went on to become one of my best students, co-authoring twelve scientific publications with me over the next four summers. Robert went on to earn his MD and Ph.D. degrees at the Johns Hopkins University School of Medicine in Baltimore.

In 1992, Dr. D'Amato, now an ophthalmologist finishing his training at the Massachusetts Eye and Ear Hospital discovered that blindness, like cancer, depended on the growth of new blood vessels. In blindness arising out of diabetes or age-related macular degeneration, new blood vessels grow in the retina of the eye and block vision. In cancer, new blood vessels sprout to feed the growth of tumors. Dr. D'Amato wondered if there were existing drugs that could stop the growth of new blood vessels without affecting existing ones. In this vein, he explored whether drugs causing birth defects or changes in reproductive cycles in women did so by blocking the growth of new blood vessels. His search suggested the possibility that the drug thalidomide, a drug scorned for its effects in causing deformed children in the early 1960s, might provide the answer.

Teaming up with Dr. Folkman, the father of angiogenesis, the two explored the idea. Soon Dr. D'Amato succeeded in convincing Dr. Folkman that thalidomide may be an antiangiogenic drug worth further investigation. Dr. D'Amato demonstrated thalidomide's effects in blocking new blood vessel growth and the findings were published in the *Proceedings of the National Academy of Sciences* in April 1994. Within less than four years, our team at EntreMed, in concert with the National Cancer Institute, took this early concept through Phase II studies in cancer patients and obtained clinical data to authorize orphan drug designation from the Food and Drug Administration for the use of thalidomide in the treatment of certain forms of cancer.

We knew that it would take years for us to bring thalidomide into routine patient use due to the notorious history of the drug and the requirements for arduous clinical testing by the Food and Drug Administration. As such, we sought a large pharmaceutical partnership to help speed the process. We licensed thalidomide to Bristol Myers Squibb, the world's largest cancer company, while continuing our clinical trials. They decided that the challenge was too daunting, and returned thalidomide to us after a year of study. Fortunately, we learned that another small biotechnology company, Celgene, in Warren, New Jersey, recently obtained orphan drug designation from the FDA for the use of thalidomide in treating leprosy and felt they might be right for this use as well. In December 1998, we reached an agreement between EntreMed and Celgene that allowed thalidomide to be prescribed by physicians on an "off label" use for cancer, accelerating its availability to patients by at least three years.

After promising laboratory results at Children's Hospital and EntreMed, pioneering clinical studies by Dr. Bart Barlogi in Arkansas and Dr. Ken Anderson in Massachusetts, who is here today, thalidomide has shown its benefit in treating patients with multiple myeloma.

Mr. Chairman, as the "Angiogenesis Company," EntreMed is dedicated to uncovering new treatments for cancer, including cancers of the blood. We have shown that angiogenesis in the bone marrow plays a major role in the progression of these "liquid tumors," causing bone erosion and progressing the disease, and antiangiogenic drugs such as thalidomide have been shown in preclinical studies to block the progression of myelomas and leukemias.

Today, Geraldine Ferraro is doing well as a consequence of our collective efforts. We are proud of the role that EntreMed and our collaborators at Children's Hospital have played in making thalidomide available to patients with this form of blood cancer. But thalidomide is not yet approved for use in cancer, and it has limiting side effects. Right now in our laboratories and with collaborators at Children's Hospital and elsewhere, we have found new and more powerful chemical cousins of thalidomide that have fewer side effects. These promising drug candidates are moving rapidly towards clinical trials.

Dr. D'Amato also has discovered another drug, Panzem (2-methoxyestradiol); that in preclinical studies shows great promise in treating multiple myeloma. It is orally available, and was shown by EntreMed's Phase I studies in breast cancer to be without dose-limiting toxicities. Because of EntreMed's successful efforts in demonstrating the safety of this drug, Panzem is now in Phase II clinical trials in multiple myeloma patients at the Mayo Clinic in Rochester, Minnesota and further studies are to begin shortly with Dr. Anderson at the Dana Farber Cancer Institute, in Boston.

But our passion to accelerate drug discovery and approval is not an easy one. Industry statistics for drug development reveal a daunting challenge. According to the Pharmaceutical Research and Manufacturer's Association, on average only one in 5,000 potential drug discoveries results in an approved drug twelve years later, at a cost in excess of $400 million. Biotechnology companies are trying to discover and develop drugs better, faster, and cheaper, and we are highly creative in addressing unmet medical needs. Unlike big pharmaceutical companies, however, we have limited resources.

Despite their potential to revolutionize medicine, from the financial perspective, drug discovery and development efforts in biotechnology are by their very nature risky, capital intensive and protracted. The search for new drugs by biotechnology companies is like drilling for oil or prospecting for gold. There are no guarantees, and they are not always successful in developing products and rewarding their shareholders that took the financial risk. We seek your assistance in this effort. We are succeeding at providing exciting new solutions to deadly diseases that have gone unsolved for far too long. We need Congress' help in continuing.

Failure to nurture these new revolutionary new discoveries is like leaving ripe apples in the orchard. Dr. Alexander Fleming is said to have sadly lamented: "Penicillin sat on my shelf for 12 years while I was called a quack. I can only think of the thousands who died needlessly because my peers would not use my discovery." We need to open minds to invent new ways of attacking cancer, such as angiogenesis. In the war on cancer, the battlefield tactic of blocking blood vessel growth is like attacking the enemy's supply lines.

Mr. Chairman, in record time EntreMed has taken antiangiogenic drugs like thalidomide into the clinic. Now, cancer patients receiving Endostatin™ infusions in our Phase I human trials in the United States and Europe are showing no adverse events while some patients have achieved disease stabilization and tumor responses in studies designed only to assess the safety of our drugs. Panzem® is now in Phase II studies in patients with multiple myeloma and prostate cancer. We are making great progress in realizing our goal of "cancer without disease," where cancer patients may be able to live full lives like diabetics, but instead of receiving insulin, they will get antiangiogenic drugs.

Those of you with cancer or with family or friends who suffer from the scourge of this disease know all too well the frustration and helplessness of waiting for breakthroughs to become a reality. We hear the cry of the dying mother, father, sister, brother, and friend. Now we must commit the resources to win the war on cancer, and to reaffirm our country's prominence as the world's leader in technology and science. We can no longer afford to be patient. We must apply the strategies and tactics of the battlefield to scientific discovery and development in order to win this war on cancer. It is absolutely essential that we have your help in this great battle.

With your help, Chairman Harkin and all the members of this Committee, we cart carry on the fight with promising new cancer strategies through the provision of greater resources to researchers and biotechnology companies. Now is the time to invest in research that will save the lives of our loved ones. This is a war that must be won now!

Thank you Mr. Chairman.

Senator SPECTER. Thank you very much, Dr. Holaday.

We have 8 minutes remaining until blackout time at 11:30 and two Senators with rounds of 4 minutes each. Senator Hutchison.

Senator HUTCHISON. Well, thank you. I will be just very brief.

I would just like to use my time to ask you, Dr. Holaday, to expand on the trial or study that is going on at Mayo and what you hope to gain from that that you do not have with thalidomide today.

Dr. HOLADAY. We think that the approach towards any drug discovery process has to be multifaceted, and this particular molecule,

Panzem, also known as 2-methoxyestradiol, is a natural substance that has shown great promise in preclinical studies in treating various forms of multiple myeloma at the experimental level. Based upon that promise and the fact that it showed no dose-limiting toxicities in phase I studies in breast cancer at Indiana University, we were encouraged to proceed rapidly and move that into phase II studies at the Mayo Clinic to see if what we see in the animal models is also true in people. And we are very encouraged by what we are seeing to date.

Senator HUTCHISON. Would it be more of a cure or a treatment?

Dr. HOLADAY. We would like to encourage the consideration of these new treatments as allowing people to have cancer without disease, much as Dr. Anderson said, maybe diseases like diabetes where you live with your insulin and you do not die from the disease. I think that as we look modestly at our future, we should consider that these molecules like thalidomide, analogs of thalidomide, and Panzem are going to offer us that opportunity.

Senator HUTCHISON. Well, thank you. I just once again want to thank all of you. Every one of you on the panel has offered something wonderful: Geraldine Ferraro for helping us start this awareness which Senator Mikulski and I and Senator Specter are going to try to continue; and Kathy Giusti, for your early pioneering efforts when you did not have a whole lot of support, but now I think you do; and Dr. Holaday and Dr. Anderson for your commitment. We certainly look forward to working with each of you to find a cure for each of these diseases. Thank you.

Senator SPECTER. Thank you, Senator Hutchison.

Senator Mikulski.

Senator MIKULSKI. Thank you very much, Mr. Chairman.

Just very briefly. First of all, I am so proud of my friend, Geraldine Ferraro, who has taken a very private matter and taken this as usual with her wit to come forward and turn this into a matter of public advocacy, both for research, as well as encouraging people to be bold and courageous enough to do the early detection. Of course, Dr. Holaday is the CEO of one of our biotech firms in Maryland, and we had an excellent conversation the other night.

Mr. Chairman, I am going to have maybe one question for Dr. Holaday.

But this is a very emotional hearing for me and I think for everybody because many of the people in this room we know personally. I can tell you exactly where I was on a Sunday morning when Geraldine Ferraro called me to tell me about this disease. I literally could not believe it. I am home Sunday morning drinking coffee. Gerry and I periodically talk on Sundays. And she said, Barbara, I have blood cancer. It took my breath away. So, we immediately talked about how to be supportive.

Second, later on when she told me she was on thalidomide, I said, Gerry, this is about birth defects. Again, I was shocked.

The reason I say all of this is that when cancer affects someone, it affects family and it affects friends. Part of the cure I believe is in family and friends. So, we are all in this together. Gerry, we want you to know I think all of America, Larry, and Ms. Giusti and all who testified, that you are part of an American family, and we are just going to pull for you. This is not about being a Democrat.

This is not about being a Republican. This is about being part of an American family and really seeing what we can do to help you. So, we thank you.

And Dr. Holaday, we want to have other conversations with you on how we can encourage biotech. Not all research is going on at NIH. We need to have a continuum of research. We need to have policies and tax breaks for research and development to really have these breakthroughs.

My only concluding remark is to the doctors, to the scientists, to the patients, may the force be with you and may God be with the United States Senate to help you. Thank you.

Senator SPECTER. I thank you very much, Senator Mikulski, and thank you all, all the witnesses, for a very extraordinary hearing. I thank you, ladies and gentlemen, for being here and for your enthusiasm. Now our work is cut out for us to get increases in funding for the National Institutes of Health and to get Federal support for stem cell research so that we can move ahead to solve these tremendous problems.

We have received written statements that we will include in the record.

[The statements follows:]

PREPARED STATEMENT OF BEVERLY S. MITCHELL, M.D., PRESIDENT, AMERICAN SOCIETY OF HEMATOLOGY

Senator Harkin and members of the Subcommittee, thank you for holding this very important hearing today on the hematologic malignancies. My name is Beverly Mitchell and I'm Chief of the Division of Hematology and Oncology and Associate Director of the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill. I am President of the American Society of Hematology (ASH), which has over 10,000 scientists and clinicians united by their common interest and commitment to understanding and curing blood disorders. The Society thanks the Subcommittee for their unwavering support of biomedical research and fully supports the Ad Hoc Group for Medical Research Funding recommendation of an appropriation of $23.7 billion for the National Institutes of Health in fiscal year 2002.

ASH is proud that NIH-sponsored research in hematology has led to important discoveries with broad applicability to treating heart disease, strokes, end-stage renal disease, cancer and AIDS, among other human diseases. For this reason, the Society is firmly committed to broad-based support for biomedical research and to the existing peer-review process as the best way to identify and prioritize scientific grants. Since the study of blood and its disorders involves a number of areas, hematologists receive funding from multiple NIH Institutes. The Society would like to particularly commend the leadership of the NHLBI, NIDDK, and NCI for their vision and superb stewardship.

I would specifically like to congratulate Dr. Richard Klausner and his colleagues at the NCI as well as the many scientists, clinicians, and advocates that worked on the Leukemia, Lymphoma, and Myeloma Progress Review Group, also known as the blood cancers PRG. Historically, research in the blood cancers supported by NCI has provided the biological framework for new directions and progress in the research and treatment of all cancers. Now, the convergence of new tools and technologies presents us with the opportunity to place discovery and development of cancer prevention and treatment interventions on a firm scientific footing. There is a sense of excitement in the hematology community particularly with the rapid evolution of molecular biology that has already led to a number of major discoveries. The Lymphochip, for instance, is a DNA microarray that gives us an unprecedented view of the molecular machinery of blood cancer and will be used to study samples of thousands of patients with all varieties of lymphoma and leukemia. You have also heard of Gleevec, or the leukemia pill, which offers effective new treatment for chronic myelogenous leukemia or CML.

It is on the heels of these and of other important discoveries that the NCI's blood cancers PRG completed its excellent review of the basic science and clinical challenges to advancing our understanding of the blood cancers. The report is incredibly

comprehensive, covering not only issues in basic biology and clinical trials methodology, but also epidemiology, collaboration, education, communication, and behavioral and outcomes research. Immediate priorities identified in the report include increased understanding of the basic biology and the key environmental factors that lead to blood cancer, increased translational research resources, identifying populations at high risk, and improving access to quality care through accurate and timely distribution of information and increased training of physicians. The centerpiece of the report is the development of a Cancer Translational Research Allied Consortium to bring together academia, industry, government, and patients to shorten drug development time for the hematologic cancers from between 5 and 10 years to 2 years.

The American Society of Hematology strongly urges that a budget and business plan be developed to guide implementation of the blood cancers PRG report recommendations. ASH is concerned that without such a plan, specific steps for collaborative action to accelerate the development of new therapies for blood-related cancers will go unidentified.

A budget and business plan would help us increase our understanding of myelodysplasia, for example. Myelodysplasia is a serious disorder that occurs in older patients and in individuals who have undergone previous radiation or chemotherapy treatment for cancer and/or blood diseases such as aplastic anemia. Standard treatment is currently limited to blood product transfusions, and, in some cases, chemotherapy treatments if the disease develops into acute leukemia. There is no curative treatment other than bone marrow transplantation, which is effective in only a small percentage of patients. Among the victims of myelodysplasia are the astronomer and great promoter of science, Carl Sagan. Also, at the end of his life, your former colleague, the honorable Senator Paul Tsongas, battled myelodysplasia that developed as a result of the treatment that he received for his lymphoma. As the lifespan of the average American increases, myelodysplasia, a formerly rare disorder, is becoming more common. A budget and a blueprint for the PRG will lead to recognition and support for research that will help us find ways to further unravel the mystery of myelodysplasia so that we are able in turn to extend the lives of patients, many of them already survivors of cancer and other devastating diseases.

In addition to urging you to support these important follow-up activities to the tremendous PRG effort, I would also like to take this opportunity to highlight an important legislative effort in the reimbursement arena that complements the scientific progress in treating blood cancer. I would like to bring to your attention the Access to Cancer Therapies Act of 2001, introduced by Senator Olympia Snowe and Representative Deborah Pryce. If enacted, the legislation would update Medicare's reimbursement policy to cover all oral anti-cancer drugs since Medicare currently only pays for an oral cancer drug if it has an equivalent that can be administered intravenously, incident to a physician's service in a doctor's office or in a hospital outpatient department.

The American Society of Hematology strongly urges you and your colleagues to sign-on as a co-sponsor of the Access to Cancer Therapies Act to help ensure its passage in this session of Congress.

The Access to Cancer Therapies Act is critical in particular because new oral anticancer drugs are emerging as an indispensable feature of quality cancer care and will replace or make more effective current therapies largely based on intravenous administration. Today, these and other oral cancer treatments are only 5 percent of the market, but are expected to increase to 25 percent or more by the end of this decade. Furthermore, without Medicare coverage, most of these oral drugs will require out-of-pocket payment and access for cancer patients will be unfairly influenced by the patient's ability to afford these new approaches to treatment. For many cancer patients, especially those in rural areas, oral drugs are not only preferred, but are absolutely necessary as life-extending treatment.

In conclusion, this is an exciting time to be engaged in biomedical research and we are proud that ASH members are participating in so many innovative studies. ASH applauds the excellent stewardship of the hematology research portfolio, particularly at the NCI. The opportunities in hematologic malignancy research are immense. I believe that with a budget and a blueprint for implementing the recommendations of the PRG, the effort will stimulate the necessary partnerships and cooperative ventures involving multiple academic centers for clinical research projects to succeed in bringing improved therapies for patients. At the same time, we must make sure that mechanisms for reimbursement, such as that provided by the Access to Cancer Therapies Act, are in place so that patients can receive the very best in cancer treatment.

ASH sincerely hopes that you will be able to continue your longstanding policy of support for cancer research and access to quality cancer care.

PREPARED STATEMENT OF HOWARD B. URNOVITZ, PH.D., SCIENTIFIC DIRECTOR, CHRONIC ILLNESS RESEARCH FOUNDATION AND CHIEF SCIENCE OFFICER, CHRONIX BIOMEDICAL

Mr. Chairman, I am grateful to the Committee for allowing me the opportunity to submit written testimony in support of this hearing being held to examine issues regarding blood cancers such as leukemia, lymphoma, and myeloma. After receiving my doctorate degree in Microbiology and Immunology from the University of Michigan in 1979, I did a postdoctoral fellowship at Washington University School of Medicine, St. Louis, studying research models for multiple myeloma. Currently, I am Scientific Director of the Chronic Illness Research Foundation and Chief Science Officer of Chronix Biomedical, a privately owned company conducting research focused on identifying predictive, diagnostic and therapeutic genomic markers and targets in chronic diseases.

I am providing this testimony to emphasize the importance of providing effective laboratory markers in clinical trials of new multiple myeloma therapeutic management strategies. The correct selection of laboratory markers can ensure the most effective treatment, thereby maximizing drug efficacy and minimizing adverse effects.

Multiple myeloma is like most chronic illnesses with respect to its unknown origins and progressive mechanisms. This disease can remain asymptomatic or smoldering for many years. In the symptomatic phase the most common complaints are bone pain and fatigue. Treatment improves the clinical situation in only about 60 percent of the patients. Multiple periods of remission and relapse can occur. Currently the disease is incurable.

In December 2000, Dr. Brian G. M. Durie and I reported on the discovery of a new surrogate marker for Multiple Myeloma ("RT–PCR Amplicons in the Plasma of Multiple Myeloma Patients Clinical Relevance and Molecular Pathology," *Acta Oncologica* Vol. 39, No. 7, pp. 789–796). Dr. Durie has written over 250 myeloma research papers, as well as numerous book chapters. He is Chairman of the Board and Scientific Advisor to the International Myeloma Foundation (www.myeloma.org), which he co-founded with Brian and Susie Novis. Dr. Durie is a Professor of Medicine and on staff at Cedars Sinai Comprehensive Cancer Center, Division of Hematology—Oncology, Cedars Sinai Medical Center, Los Angeles, CA.

Our publication, which is submitted along with this testimony, describes the surprising discovery of genetic material, RNA, in the plasma (i.e., the cell-free portion of the blood) of multiple myeloma patients. RNA is part of the genetic machinery of our bodies and is rarely detected outside of cells. We identified the RNA as being part of the recently mapped human genome. The most important observation of this study was that the detection of a specific RNA marker seemed to correlate with the clinical status of the patient, that is, to relapse or remission. In patients who were in remission in response to successful treatment, the RNA marker became undetectable; in those patients in whom treatment was unsuccessful, the RNA marker continued to be detected in their plasma.

Since the publication of this study, we have applied these new methods derived from the information catalogued by the Human Genome Project to identify many more RNA markers in other chronic diseases. With support from Dr. Durie and the International Myeloma Foundation, our preliminary data suggest that plasma RNA expression profiles will be strong candidates for monitoring the success or failure of drug therapies. My colleagues and I feel that the introduction of new concepts in identifying surrogate markers will have a strong impact on our fight against cancer.

I want to thank the Committee for its attention in addressing the need to provide early detection and more effective treatments in the battle being waged against debilitating chronic diseases, particularly multiple myeloma.

PREPARED STATEMENT OF MRS. RAFAEL MORA

I am submitting testimony on behalf of my spouse who went home to the Lord on April 26, 2001 who had multiple myeloma cancer. My spouse began to have back pain in the beginning of the year 2000, and we sought medical attention immediately through our HMO. Numerous delayed appointments took place, followed by mis-diagnosis such as back injury, muscle spasm, skeletal, disc, hernia, sciatic nerve, etc. Finally some tests, and labs were done and not until June 2000 was the

cancer diagnosed at the Washington Cancer Institute, where our HMO had finally referred us to after wasting so much precious time.

We began radiation immediately followed by chemotherapy. The goal was for my spouse to receive a bone marrow transplant which would take place at John Hopkins Hospital in November 2000. My spouses care was coordinated through our HMO and Johns Hopkins Hospital. Just before the transplant was to take place we were informed by John Hopkins that lab results done 3 weeks earlier by our HMO—had only now been received from our HMO—and it showed "enzymes" rising in my spouses liver and we would need to postpone the bone marrow transplant and begin chemotherapy immediately. John Hopkins said that we needed to monitor my spouses liver, because if his liver was not "normal" it would be fatal to move forward with the bone marrow transplant. On January 7—the 4th cycle of chemotherapy ended and my spouse was scheduled for a liver biopsy which did not take place till January 18 because he became ill with a bad cold. On Feb. 8 we received via e-mail from John Hopkins—a message that it would be fatal to move forward with the bone marrow transplant because his liver was not normal for a transplant after reviewing tests and conferring with other liver/pathologist specialist. I and my spouse believed the chemotherapy caused the damage to liver.

By this time we were unable to participate in any clinical studies due to my spouses stage of disease and John Hopkins recommended thalidomide treatment as the next course in treatment and our HMO agreed. However, the thalidomide treatment did not begin till 2 months after the chemotherapy had ended because the HMO doctor was out of town and no one else could write the prescription for thalidomide, although now—they say otherwise.

Amazingly with all the cruel delays, the treatment of thalidomide showed very hopeful results. However, my spouse began taking new pain medicines on April 10 and became violently ill on April 19. We sought medical attention with our HMO and was told "it was the myeloma and that we needed to manage the pain". We did not agree and we did not take anymore of the pain medicines. My spouse continued to eat and drink fluids and have bowel movement but one day later he awoke disoriented and we went to the hospital emergency. The 3 doctors on duty informed us that his kidneys had shut down and they were trying to save him. Those physicians at the hospital felt that most likely the pain medicines my spouse received, had caused his kidneys to shut down—we would not know for certain till a biopsy of the kidneys were done. For the first 3 days in the hospital my spouse continued to eat and have bowel movement and although it looked like his kidneys were recovering, dialysis was ordered by the two attending physicians. One physician stated "you will die without dialysis". On April 25 a port was placed on the right side of my spouses upper chest in the vein that runs from the neck area. It was not properly placed and my husband hemorrhaged for 12 hours. We were also told that the injection of heparin he received during his dialysis caused the bleeding which they continued to refer to as "an ooze". My husband went into shock at 1:30 a.m. and held on till 8:15 p.m. the next evening when he went home to the Lord on April 26, 2001.

Our son never had the opportunity to have that crucial important time with his father before he went home to the Lord. My spouse suffered in the hospital due to the severe inadequate care. His diagnosis was well late into the disease because of the seriously inadequate health plan services we received from our HMO—constant delays of appointments, testing and lab services.

All of this should not have happened. It has been a terrible, terrible, painful and hurtful experience. My spouse was 60 years old, he was a very active and fit person all his life and even after the disease struck him he continued to do all that he could to help beat this cancer. Our 13 year old son is still in trauma and when he grieves for his father he gets a nose bleed. He is afraid to cry because of the nose bleed. Our family has been devastated.

The HMO health service and the Hospital health service received is shameful and will never be forgotten. This has been a nightmare. I hope this hearing will bring to light how many people have suffered, and their families because of health insurance providers, doctors and staff that are not specialized to handle cancer cases, who however, continue to treat patients and write prescriptions as if every person were just a number.

So what do I hope this testimony will accomplish? I hope and pray that no more people will have to suffer due to wasted precious time by going to their physician, HMO or health insurance provider. I urge everyone to get into a cancer center immediately if there is any hint that you may have something cancerous or unexplainable. These cancer centers specialize and have the great experience needed in the battle against cancer, and yes it is a battle. These cancer centers will do all that they can for you. They will not let you suffer and lie to you. They will not give

you pain medicines without warning you that your kidneys could give out—they know exactly what you should receive and what you should not. And if any problems arise they will have exact history and be able to treat you immediately without guessing or suggesting it is your disease. These cancer centers have very serious, well educated doctors, researchers and staff who desperately are trying to find cures to help people. They have controlled environments and understand and know what patients need and they are comforting. I firmly believe that what my spouse and many, many others have to go through would not happen at these cancer centers. You may ask how do I know these things. Well, althrough my spouses battle we continued to educate ourselves and looked into any study we could find and read up on numerous cancer centers in this country from the west to the east coast, and other countries as well and what they are doing. Our desk at home is a huge pile of cancer studies, research and information.

I must mention that by having my spouse go through all those meaningless appointments in the beginning with the HMO and holding out to refer him to a cancer center just to save a few pennies was the worse situation ever encountered. That is why our health care system is so burdened because instead of getting to the root of problems, precious time is being wasted and money, by making clients go through a song and dance with their very own lives.

My spouse, our sons father—can never be replaced. It is a sorrow that will live with us. More funding is crucial for cancer centers around the nation and world providing specialized treatment in cancer. In closing, according to NBC news release on May 11, 2001, over 98,000 deaths occur each year due to prescription medicines (the pain medicine oxycotin was the feature story). We are still waiting for the full autopsy report from the hospital.

Let us not waste precious time—IT IS A RACE FOR THE CURE.

CONCLUSION OF HEARING

Senator SPECTER. Thank you all very much for being here, that concludes our hearing. The subcommittee will stand in recess subject to the call of the Chair.

[Whereupon, at 11:28 a.m., Thursday, June 21, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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