DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 8 and 9, 1993

Building 31, Conference Room 10
National Institutes of Health
Bethesda, Maryland

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
February 8 and 9, 1993

The National Cancer Advisory Board (NCAB) convened for its 85th regular meeting at 8:00 a.m., February 8, 1993, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg
Mrs. Zora Brown
Dr. Kenneth Chan
Dr. Pelayo Correa
Dr. Robert W. Day
Mrs. Barbara P. Gimbel
Mrs. Brenda Johnson
Mrs. Marlene A. Malek (absent)
Ms. Deborah K. Mayer
Dr. Sidney Salmon
Dr. Ellen V. Sigal
Dr. Howard M. Temin
Dr. Samuel A. Wells, Jr.
Dr. Charles B. Wilson

President's Cancer Panel

Dr. Harold P. Freeman (Chairman)
Mrs. Nancy G. Brinker
Dr. Henry C. Pitot

Alternate Ex-Officio NCAB Members

Captain Bimal C. Ghosh, DOD
Dr. John Johnson, FDA
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Sheila Newton, NIEHS
Dr. P. C. Srivastava, DOE
(for Dr. John C. Wooley)
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Daniel Ihde, Deputy Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management
Mrs. Barbara S. Bynum, Director, Division of Extramural Activities
Dr. Bruce A. Chabner, Director, Division of Cancer Treatment
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Werner Kirsten, Associate Director, Frederick Cancer Research and Development Center
Dr. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Mrs. Iris Schneider, Executive Secretary, Assistant Director for Program Operations and Planning

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[1] For the record, it is noted that members absented themselves from the meeting when discussing applications (a) from their respective institutions or (b) in which conflict of interest might occur. The procedure does not apply to *en bloc* actions.

Liaison Representatives

Dr. Eve Barak, Associate Director for Cell Biology, Division of Cellular Biosciences of the National Science Foundation, representing the National Science Foundation, Washington, DC.

Ms. Stacey Beckhardt, representing the American Society of Clinical Oncology, Inc. (ASCO), for Dr. Gelmann.

Dr. R. Davilene Carter, representing the American Association for Cancer Education.

Mr. Alan Davis, representing the American Cancer Society (ACS).

Dr. Robert W. Frelick, Past President, Delaware State Tumor Registry, representing the Association of Community Cancer Centers.

Ms. Pamela Haylock, representing the Oncology Nursing Society (ONS) for Ms. Curtiss.

Dr. Edwin A. Mirand, Associate Director and Dean, representing the Association of American Cancer Institutes.

Dr. Warren Pearse, representing the American College of Obstetricians and Gynecologists.

Mrs. Yvonne Soghomonian, representing the Candlelighters Childhood Cancer Foundation.

In addition to NCI staff members, meeting participants, and guests, a total of 20 registered members of the public attended the meeting.

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I. CALL TO ORDER AND OPENING REMARKS—DR. PAUL CALABRESI

Dr. Calabresi called to order the 85th meeting of the National Cancer Advisory Board (NCAB) and expressed the Board's sympathies to the families of several recently deceased members of the NCI community, including Dr. Werner Kirsten, Associate Director of the Frederick Cancer Research and Development Center; Dr. Thelma Dunn, pathologist and scientist; and Dr. Frank Rauscher, former NCI Director. He asked Board members and others present to rise and observe a moment of silence for these individuals and their families.

Dr. Calabresi introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. Dr. Calabresi asked for the Board's approval of proposed NCAB meeting dates for 1994; hearing no objections, he stated that the dates stand as confirmed. He then called for approval of the minutes of the previous meeting, which were unanimously approved without change.

Dr. Calabresi called Board members' attention to a booklet entitled *Principles and Standards of Ethical Conduct* distributed to them in accordance with the Ethical Reform Act of 1989. The Office of Government Ethics, he explained, implemented new uniform standards of conduct on February 3rd, 1993, and has mandated that every Federal employee be given the opportunity to review these new standards. Because members of the NCAB and the President's Cancer Panel have the legal status of Federal employees while serving in their official capacities, Dr. Calabresi asked Board members to review this booklet during the meeting, sign the accompanying certification of compliance, and return the certification to Mrs. Barbara Bynum. He added that members could discuss any concerns regarding these issues with Mr. Donald Christoferson, who serves as NCI's Deputy Executive Officer and Acting Ethics Official.

Dr. Calabresi reported that, due to the absence of Dr. Harold Freeman, the report of the President's Cancer Panel would be postponed until the May NCAB meeting.

II. REPORT OF THE DIRECTOR, NCI—DR. SAMUEL BRODER

Dr. Broder called the Board's attention to a list of NCI personnel changes that had been distributed. He announced that Dr. Richard Adamson, Director of the Division of Cancer Etiology, is serving as Acting Associate Director of the Frederick Cancer Research and Development Center following the December 24th death of Dr. Werner Kirsten. Dr. Broder noted that Dr. Kirsten, a pathologist, had investigated retroviruses as a cause of cancer; he discovered a virus that became known as the Kirsten sarcoma virus and this work led to the discovery of a viral gene named *K-ras* in his honor. Dr. Kirsten also held voluntary positions with the American Cancer Society (ACS), the Leukemia Society, and the Damon Runyon/Walter Winchell Fund for Cancer Research.

Dr. Broder introduced a new NCI staff member, Dr. Maureen Wilson, who will serve as Ethics Officer and Executive Secretary for the President's Cancer Panel. He thanked Mr. Donald Christoferson for having served as Acting Ethics Officer and Ms. Iris Schneider for having served as Acting Executive Secretary for the President's Cancer Panel.

In the Division of Cancer Prevention and Control (DCPC), Dr. Broder continued, Dr. Barry Kramer, Associate Director of the Early Detection and Community Oncology Program, has been promoted to the Senior Executive Service. In the Division of Extramural Activities (DEA), Ms. Toby Friedberg, for several years a chemist in the Research Analysis and Evaluation Branch, has been appointed as the Institute Referral Officer in the Review Logistics Branch of DEA. In the Division of Cancer Treatment (DCT), Dr. Matti Al-Aish, Chief of the Diagnostic Imaging Branch, has retired; Dr. Jim Mule of the Surgery Branch has left to head the research group of the Systemics Corporation in Palo Alto, California; and Dr. Dave Poplack, head of the Pharmacology and Experimental Therapeutics Section of the Pediatrics Branch, has left to become Director of the Baylor College of Medicine Children's Cancer Center.

Dr. Broder announced that two new sections have been established within the DCT's Cancer Therapy Evaluation Program—the Developmental Clinical Trials and Preclinical Studies Section and the Clinical Trials Section. Two new sections have also been established within the Pediatric Branch of the DCT's Clinical Oncology Program—the Cellular and Molecular Biology Section and the Molecular Oncology Section. The Molecular Genetics Section, Dr. Broder added, has been eliminated. A Gynecologic Oncology Section has been added to the Surgery Branch.

Dr. Broder noted that Dr. Frank Rauscher, who died of a heart attack on December 31st, had worked at the NCI from 1959 to 1976, serving as Director from 1971 to 1976. Dr. Rauscher played a major role in the development of the Institute's program on viral oncology; after leaving NCI, he directed a research program for the American Cancer Society and later joined the Thermal Insulation Manufacturers' Association to work on the development of a noncarcinogenic material to replace asbestos.

Dr. Broder reported that on January 6th, at a meeting of U.S. and Japanese researchers on retroviruses and cancer hosted by the NCI, he suggested in his welcoming statement that the meeting be dedicated to Drs. Kirsten and Rauscher to acknowledge their leadership and scientific contributions in the area of viral oncology. He expressed his hope that future scholarly presentations or meetings would also be dedicated to these individuals.

Dr. Broder announced the recent deaths of two other former NCI employees. Dr. Thelma Dunn, a leading cancer pathologist, worked at the NCI from 1942 until her retirement in 1970. Dr. Leonard H. Scheele, who was the NCI's third Director and also served as a U.S. Surgeon General, began his career as a cancer fellow at Memorial Hospital in New York City and served NCI as an officer in charge of the National Cancer Control Program from 1939 to 1942; he served as NCI Director from 1947 to 1948.

Dr. Broder moved on to report some positive administrative actions. In December, the Food and Drug Administration (FDA) approved taxol for the treatment of refractory ovarian

cancer. The NCI played a pivotal role in the development of this promising drug, which is also active in breast cancer, lung cancer, and lymphoma. Prior to approval, taxol was provided on a compassionate basis to 1,700 women with refractory ovarian cancer at no charge, and will soon be made available on the same basis to women with refractory breast cancer.

Dr. Broder added that Bristol-Meyers-Squibb recently announced that, due to their success in the alternate production of taxol, it will not be necessary to harvest bark from the Pacific yew in Federal forests this year. Approximately 1.6 million pounds of bark were harvested last year, and it had been estimated that bark from Federal lands would be needed through 1995. The company, which is licensed to develop taxol for the NCI, is now synthesizing taxol from a precursor found in European and Himalayan yew trees.

Dr. Broder reported that the President's Cancer Panel's Special Commission on Breast Cancer met on January 11th and 12th in Atlanta to discuss issues related to treatment, psychosocial factors, and rehabilitation. The NCI also sponsored a meeting on breast cancer in young women on January 28th. Dr. Broder pointed out that although women under the age of 40 are less likely to develop breast cancer than older women, the disease can be quite virulent among those younger women who do develop it. Breast cancer is the leading cause of death among women between the ages of 40 and 44, and breast cancer patients under the age of 35 have the poorest survival rate of any age group. Dr. Broder noted that 11,000 women under the age of 40 who were diagnosed with breast cancer last year represent about 6.2 percent of the total number of breast cancer cases.

This NCI-sponsored meeting, he continued, addressed basic and clinical research as well as practical issues relating to the prevention, diagnosis, and treatment of breast cancer in young women. Questions were raised concerning the efficacy of mammography among this age group and the causes of the increasing incidence of breast cancer among young women, as were questions about pregnancy, breast reconstruction, exogenous estrogen, and birth control pills for breast cancer survivors. The proceedings of the meeting will be published in a *Journal of the National Cancer Institute* monograph.

Dr. Broder highlighted the fact that the Institute's Physician Data Query (PDQ) computerized system lists 175 protocols for breast cancer clinical trials currently supported by the NCI and related groups, ranging from prevention and intervention to drug resistance to gene therapy. He also noted that the general decrease of 12 percent since 1973 in the breast cancer death rate among White women under the age of 50 is an encouraging indication that progress is possible.

The NCI, Dr. Broder announced, will host an international workshop on screening for breast cancer on February 24th and 25th, to be chaired by Dr. Susanne Fletcher of the American College of Physicians. Participants will review worldwide clinical trial data on breast cancer and assess the current state of knowledge and future research needs, focusing on issues such as physical examination, imaging technologies, and radiation risk. The Special Commission on Breast Cancer will meet in Washington on February 23rd to discuss factors affecting the development of new agents to prevent, diagnose, and treat breast cancer and the rates charged by the biotechnology and pharmaceutical industries for these agents. Dr. Richard Travis of the U.S. Army and Dr. Joseph Cassells of the Institute of Medicine will

speak to the Commission on the plans for utilizing the approximately $200 million appropriated to the Defense Department for breast cancer research. On March 18th and 19th, the Special Commission on Breast Cancer will meet in Miami to discuss screening, early detection, and new technologies for detection and diagnosis.

Turning to the present NCAB meeting, Dr. Broder observed that a subtext of economics will inform many aspects of the presentations now and in the future as the Institute tries to ensure that its research agenda takes into consideration the many economic issues facing the country. Referring to several scientific presentations also on the meeting agenda, he added that some of the economies realized in medical care are the results of successful research; thus, he concluded, the research performed by NIH and the NCI are an integral part of the national health care program.

Dr. Broder mentioned that several new members of Congress have been appointed to the appropriations committee that oversees NIH funding. He stated that in her legislative update, Ms. Dorothy Tisevich would report on a lunch held by NIH on February 2nd to help new congressional members and their staffs become acquainted with the NIH and its components.

He also announced that in response to recently reported concerns, the NCI is launching a study on the alleged connection between the use of cellular telephones and brain tumors. The study, which will be conducted by epidemiologists in the Division of Cancer Etiology, will include both cohort and case-control methodologies.

Dr. Broder touched on important concerns being addressed by three of the NCAB's subcommittees and task forces. The Program Project Task Force will address various issues related to P01s (program project grants) versus R01s (research project grants). There will also be a Task Force to focus on clinical trials. The Planning and Budget Task Force will discuss the FY95 bypass budget; Dr. Broder asked members to use their scientific expertise to advise on the assumptions and target goals contained in this document. The Subcommittee on Women's Health and Cancer will focus on breast cancer and other timely issues; Dr. Broder said that he asked Mr. John Hartinger to present to this subcommittee a review of the bypass budget process.

Dr. Broder encouraged Board members to convey their concerns or suggestions relating to the bypass budget by May, since a published document must be prepared by September. He noted that even though the Institute rarely receives funding at levels requested in the bypass budget, the document is very effective as a scientific planning mechanism that facilitates the formulation of the Institute's priorities. The bypass budget, Dr. Broder explained, is not designed as a shorthand summary of progress but, rather, as an in-depth analysis of the Institute's scientific commitment and goals. As such, he said, it has had a strong positive effect, serving as the functional equivalent of a strategic plan. The National Institute on Mental Health (NIMH), Dr. Broder reported, has been given the authority to develop its own bypass budget based on the NCI model, and Congress is considering authorizing this mechanism for several other NIH components, including the new Office of AIDS Research.

Dr. Broder stated that he had no new specifics on the budget to report at this meeting, noting that the new administration might be planning to submit its own budget request to Congress. He suggested that further information on the administration's plans and congressional deliberations should be available by the time of the May NCAB meeting.

Dr. Broder reported that the NIH Director exercised her authority to reallocate funds for Institute budgets for emergency research on multidrug-resistant tuberculosis. Of the $10 million to be allocated for this research, the amount taken from the NCI budget is likely to be about $1.9 million. Dr. Broder expressed his belief that the NCI has been treated fairly and that this "tap" is necessary to address a public health emergency that spans the interests of all the categorical institutes of the NIH. While multidrug-resistant tuberculosis particularly affects individuals who are immunocompromised, it is a highly lethal disease that can also infect those who appear to have normal immune function. Dr. Broder suggested that the NCI is in a position to make significant scientific contributions in this area.

III. DEVELOPMENTAL AND MOLECULAR ASPECTS OF IMPRINTING—DR. WOLF REIK

Recalling that members of the Board had previously asked for presentations on topics relevant to NCI's basic research agenda from scientists of international stature, Dr. Broder introduced Dr. Wolf Reik of the Department of Molecular Embryology, Institute of Animal Physiology and Genetics Research, Cambridge, England. Before relinquishing the floor to Dr. Reik, Dr. Broder observed that a number of disease entities—including syndromes related to cancer, such as the Beckwith-Weidemann Syndrome and chronic myelogenous leukemia—may be caused by a process known as genomic imprinting. This concept, which is contrary to that of traditional Mendelian genetics, is based on the idea that the occurrence of certain diseases, as well as the pattern of the disease, may be determined by the paternal or maternal origin of an allele. This concept of uniparental disomy, or two alleles originating from one parent, Dr. Broder explained, implies that the pattern of the disease may reflect whether the genes came from the father or from the mother.

Dr. Reik thanked Dr. Broder for his overview of the subject and explained his intention to present a general lecture on imprinting—alternately referred to as parental, genetic, or genomic imprinting—and to point out its relevance for mammalian development and for genetic disease in humans, highlighting cancer-related aspects whenever possible. He began by defining imprinting, explaining that mammalian chromosomes in germ cells, during oogenesis and spermatogenesis, acquire imprints that are epigenetic modifications (in the form of DNA methylation, for example). These imprints, Dr. Reik stressed, are not differences in DNA sequence, but are epigenetic labels that can be put onto DNA and can also be taken off again.

When these chromosomes come together at fertilization and cell division begins, Dr. Reik continued, maternal and paternal imprints are stably replicated. Imprints, therefore, are clonally stable and somatically heritable, and cells even in adult individuals retain these imprints that indicate the maternal or paternal origins of their chromosomes. The long-term

memory that indicates the maternal or paternal origin of genes may have important consequences for the function and expression of these genes in our bodies. Dr. Reik added that imprinting must also be reversible from one generation to the next; if a male individual has chromosomes with maternal imprints, these imprints must be removed during spermatogenesis and replaced with paternal imprints. While it is possible for imprints to be added onto chromosomes, it must also be possible for them to be removed in the next generation so that the chromosomes can be relabeled with the parental origin in that generation. Dr. Reik pointed out that this has important consequences for gene expression and inheritance. For example, the gene for insulin-like growth factor-2 (IGF-2), an embryonic growth factor, is expressed almost exclusively from one parental chromosome and almost totally repressed on the other parental chromosome.

Dr. Reik described the results of an experiment that examined the inheritance of a phenotype using nose size as an analogy. In one example, a mother with a small nose and a father with a large nose produced an offspring with an intermediate nose; in another example, one parent with a large nose and one with a small nose produced two offspring with large noses. These examples illustrate familiar Mendelian patterns of codominant and dominant inheritance, respectively. Another example illustrated a pattern not explained by Mendelian genetics, in which the father had a large nose and the mother had a small nose. When the small nose was the maternal phenotype and the large nose was the paternal phenotype, the offspring had a large nose; when the mother had the large nose and the father had the small nose, the offspring had a small nose. This pattern of inheritance, in which the offspring in each case resemble the father, can be explained by the mechanism of genomic imprinting.

Dr. Reik summarized an experiment to illustrate another important consequence of genomic imprinting—the fact that chromosomes are needed from both mothers and fathers. Through pronuclear transplantation, experimental mouse zygotes were produced that were chromosomally balanced, with normal diploid sets of chromosomes, but contained only all maternal or all paternal chromosomes. All of these embryos died at various stages of gestation. Dr. Reik noted that the phenotypes of the experimental embryos differed; among those with only maternal chromosomes, the embryos themselves were relatively well developed, whereas those with paternal chromosomes had better-developed embryonic membranes.

Dr. Reik stated that there is reason to believe that imprinting takes place in all eutherian mammals—that is, all mammals that have placentas. He gave as an example a slide depicting a hydatidiform mole, which resulted from a human pregnancy in which a fertilized egg lacked maternal chromosomes and had, instead, two sets of paternal chromosomes. In this case, the trophoblast—tissue that normally goes on to form the placenta—was hyperproliferative, and the fetal tissue was very disorganized.

Dr. Reik demonstrated that when experimental embryos were manipulated to extend their development into later stages, it was found that imprinting of parental information affects cell proliferation; those embryos with more paternal chromosomes were larger than controls and those with more maternal chromosomes were smaller. There was also an effect of parental programming on cell differentiation; those with more maternal chromosomes proliferated well

in neuroectodermal tissues, such as the brain, while those with more paternal chromosomes proliferated well in mesodermal tissues, such as muscle.

It is known, Dr. Reik summarized, that imprinted genes are intricately involved in regulating embryonic growth and viability and play an important role in the development and proliferation of embryonic lineages, such as the mesoderm, ectoderm, and neuroectoderm. It is important to note, Dr. Reik stressed, that there is nothing wrong with the chromosomes on which imprinted genes appear; it is the imbalance between paternal and maternal chromosomes that can cause disease. This may apply to the whole genome, as in the case of the hydatidiform mole described earlier, or to parts of the genome, usually individual chromosomes or parts of chromosomes. Recently, a number of genetic disorders have been linked to this type of imbalance, such as the Beckwith-Wiedemann syndrome, which is associated with a number of embryonic tumors.

Dr. Reik continued by explaining how it is determined that genes are imprinted. Using the example of the insulin-like growth factor-2 (IGF-2) gene, he discussed an experiment by Dr. Liz Robertson and colleagues. The IGF-2 gene, he explained, is on chromosome 7 in the mouse. A mutation was made by homologous recombination in this gene, thereby abolishing its function. Depending on whether the mutant allele was on either the paternal or maternal chromosome, the outcome and phenotype for size differed. With paternal transmission the mice were small; with maternal transmission the mice were of normal size. The normal presence of IGF-2 growth factor resulted in normal size, whereas in its absence, fetal growth deficiency occurred.

Dr. Reik displayed a slide listing the imprinted genes that have been identified—most in the mouse, and some in humans. He noted that several are growth factor genes that act during embryonic or fetal development, suggesting that the main function of imprinted genes, based on current knowledge, is the regulation of embryonic growth, development, and viability. A possible new category of imprinted genes, Dr. Reik stated, is one that is involved in RNA splicing in the brain; this gene, when it goes wrong, may influence neurodevelopmental phenotypes and, therefore, behavior after birth.

In assessing what occurs due to imprinting of the IGF-2 gene, Dr. Reik presented a slide of a mouse in which only a part of the genome was duplicated from one parent or the other. This illustrates, he said, a case of uniparental disomy in which two chromosome 7s—which are syntenic with chromosome 11p in humans—of maternal origin result in small embryos that die at later stages of gestation. Two paternal chromosome 7s, noted Dr. Reik, result in fetal overgrowth syndrome, which is relevant to Beckwith-Wiedemann syndrome. In sporadic cases of this disease, he explained, the chromosome region 11p15, which contains the gene for Beckwith-Wiedemann syndrome, is present in two paternal copies and the maternal copy is missing. It is believed, Dr. Reik concluded, that parts of this syndrome may be caused by an overdose of IGF-2 expression.

Dr. Reik noted that children with Beckwith-Wiedemann syndrome have a high risk of developing Wilms' tumor, a recessive tumor syndrome. This, he said, is due to a mutation in the tumor suppressor gene *wt1*, in which there is a loss of the normal allele and, thus, a loss of heterozygosity for the 11p chromosome associated with Wilms' tumor. Dr. Reik presented

data demonstrating that in the great majority of tumors, the maternal chromosome is lost and the paternal chromosome retained, indicating a clear influence of imprinting on tumor development. While there are a number of theories about how this occurs, Dr. Reik suggested the possibility that the overexpression of IGF-2 associated with the paternal disomy of chromosome 11 in these tumors may lead to a hyperproliferation of nephroblasts—for example, in the embryonic kidney—and then to an increased propensity for developing cancer.

Dr. Reik briefly touched on a new aspect of cancer genetics in which certain cancers are associated with reciprocal translocations; he cited as an example the Philadelphia translocation in chronic myelocytic leukemia. Recent findings have shown that the chromosomes most often involved in these translocations are the maternal chromosome 22 and the paternal chromosome 9. Dr. Reik noted that the meaning of these findings in terms of imprinting are not yet known.

Discussing the effort to determine the molecular mechanism for imprinting, Dr. Reik stated that this mechanism must be able to introduce the epigenetic marks into chromosomes at some stage during gametogenesis and to remove them in the next generation. He said that there is ample evidence from transgenic studies and those involving the X chromosome that DNA methylation is a kind of imprinting mechanism that may be involved in marking maternal and paternal genes. Using the IGF-2 gene as an example, Dr. Reik observed that there are a number of bases in the DNA that are differentially methylated in maternal and paternal chromosomes; it is not yet known whether this is the signal that determines whether or not the gene is expressed.

Another question that has not yet been answered, Dr. Reik noted, concerns identification of the genes that control imprinting. He suggested that a system to identify these modifier genes, such as a genetic assay, is needed in order to learn more about disease processes such as cancer. It is important to know which genes control the expression of the IGF-2 gene, for example, because a mutation in this modifier gene may cause the maternal copy of the IGF-2 gene to remain active, leading to Beckwith-Wiedemann syndrome and, possibly, to Wilms' tumor. Dr. Reik expressed the hope that his laboratory is close to being able to map these genes and to clone them in order to learn how they regulate imprinting.

Dr. Reik concluded by reviewing some areas for future research that he said will be important for the study of development as well as disease. First, he said, it is necessary to identify more imprinted genes; while the actual number of these genes may be small, it is important to find them because their presence in either high or low doses, as well as the occurrence of parental disomy, may lead to specific diseases. Dr. Reik reiterated that the molecular mechanism of imprinting is also under study. DNA methylation is known to be involved, and other chromatin mechanisms, Dr. Reik asserted, are certain to be involved. It is also important to define DNA sequences that confer imprinting; there must be some signal in the IGF-2 gene, Dr. Reik noted, that tells the imprinting mechanism to apply the imprint. The developmental aspects of imprinting require investigation, such as lineage-specific proliferation and differentiation and the relationship between disomy and specific diseases—for example, the Beckwith-Wiedemann, Prader-Willi, and Angelman syndromes. Research is needed on disomic lineages that arise at some stage of life due to unequal loss of parental chromosomes and can contribute to recessive tumor syndromes. Reciprocal translocations—

for example, chronic myeloid leukemia—in which there is an unequal involvement of parental chromosomes should also be studied. Finally, Dr. Reik suggested, the possibility should be considered that mutations in modifier genes may give rise to a general familial predisposition to cancer.

Questions and Answers

Dr. Temin asked whether Dr. Reik could suggest any evolutionary reason for the development of imprinting. Dr. Reik said that there are a number of possible explanations, but there is no single evolutionary theory that explains imprinting as an adaptive mechanism. The best explanation available, he said, is that during embryonic development in eutherian mammals, the higher the expression of any fetal growth factor, the more resources will be transferred from the mother to the fetus. Maternal and paternal copies of that growth factor will have different interests. Paternal copies will be directed at making the fetus grow, at whatever cost, while maternal copies will primarily influence future reproductive success and will, thus, downregulate expression of the growth factor to some extent. Over evolutionary time, this "tug of war" between maternal and paternal copies creates a stable situation.

Noting that most of Dr. Reik's examples of paternal imprinting related to childhood tumors, Dr. Calabresi asked whether any evidence suggested an involvement of maternal imprinting in tumors like breast cancer. Dr. Reik replied that he is not aware of any evidence for preferential involvement of paternal or maternal chromosomes.

Dr. Broder asked whether Dr. Reik's theory of the role of imprinting in mammals explains why parthenogenesis—the existence of viable organisms with just one haploid set of chromosomes—is possible among amphibians. Dr. Reik confirmed that this is consistent with his theory, noting that parthenogenesis is completely absent among mammals and also among seed plants, which have an endosperm tissue that is similar to the placenta. Thus, parthenogenesis is absent among organisms that have a strong nutrient transfer after conception.

Dr. Broder asked whether environmental carcinogens could cause abnormal imprinting or interfere with normal imprinting or the reversal of imprinting. Dr. Reik said that this is an unexplored area, but suggested that it is a potentially important area for study; he noted that some environmental effects on imprinting have been observed. He added that he has begun working on population genetic models to study whether environmentally altered imprints are heritable and have an adaptive function.

Dr. Henry Pitot, a member of the President's Cancer Panel, asked whether Dr. Reik's work is related to reports of imprinting by sex hormones during gestation or in early neonatal life and, if so, whether this continues for the life of the organism. Dr. Reik replied that he is not aware of the mechanisms involved in the phenomenon Dr. Pitot mentioned.

IV. REPORT OF THE DIRECTOR, NIH: WOMEN'S HEALTH AND OTHER ISSUES—DR. BERNADINE HEALY

Dr. Healy introduced her presentation by explaining that she planned to make informal comments on a variety of seemingly unconnected policy and budgetary issues that transcend politics and share a common theme: the important role played by the NCAB in shaping the future of NIH and assuring its strength. She noted that as a Presidentially appointed body, the NCAB is the most powerful advisory committee associated with NIH; it also has a strategic responsibility with regard to the bypass budget, a rare authority shared only with the NIMH and, shortly, with the AIDS program.

An illustration of the ways in which NIH is confronted with issues it has not faced in the past, Dr. Healy stated, is the unprecedented removal of $200 million from the President's NIH budget request in the past year. While it is understandable, she said, that NIH is part of the broader community and shares that community's economic problems, the reduction is hard to accept in the context of the appropriation of $200 million to the Defense Department for breast cancer research. This suggests that additional resources do exist for breast cancer research, but that they are not going to be spent at NIH. While she does not fault the fact that extra funds are being dedicated to breast cancer research, Dr. Healy expressed concern about such a substantial expenditure appearing in the budget of an agency that does not have medical research as its primary mission.

Turning to policy issues extending beyond the budget, Dr. Healy stated that although scientific integrity and misconduct issues have been quiescent recently, the community must still be aware of them. She noted that a new structure has been established outside NIH for dealing with these issues and stressed the importance of remaining involved in the handling of such matters. Conflict of interest, Dr. Healy continued, is another issue about which little has been heard lately but which also requires attention, especially in times of financial constraints. She expressed confidence in the recently developed second version of the NIH guidelines on conflict of interest, noting that the guidelines represent a strong attempt to delegate responsibility to the funded institutions for monitoring financial records for the purpose of preventing potential or perceived conflict of interest. Another principle in the guidelines, Dr. Healy stated, is a waivers mechanism that would allow critically important research by investigators with unique talents to go forward even if a perceived conflict of interest exists, assuming that proactive steps are taken to ensure that there is no distortion of research results and that the interests of the public are protected. These draft guidelines have been submitted to the Department of Health and Human Services (DHHS), Dr. Healy added, and the comments of the NCAB are welcome.

Another issue that has caused some stress, Dr. Healy continued, is the compassionate use of experimental treatments—most recently in the case of gene therapy in the treatment of brain tumors. She noted that such situations are inevitable when science moves ahead of systems that are in place. Dr. Healy acknowledged that, while other aspects of experimental therapeutics have compassionate use exemptions—the FDA, she noted, has had a system to provide such exemptions for years—NIH's Recombinant DNA Advisory Committee (RAC) lacks the expertise and guidelines necessary to deal with these matters on an emergency basis. Because the group meets quarterly and its meetings must be announced in the *Federal*

Register, there is no mechanism allowing for emergency meetings to consider requests for compassionate use of experimental therapies.

In the case of gene therapy, NIH granted an emergency waiver over the holidays after receiving the FDA's agreement. Dr. Healy pointed out that the experimental design had been approved previously by the RAC for treatment of malignant melanoma and renal cell carcinoma. Thus, a decision was made in the absence of any formal guidelines but with input from the FDA, NCI, and scientists involved in gene therapy programs. Dr. Healy concluded that these issues cut to the heart of the mission of NIH, which is not merely to do research but to work on behalf of the alleviation of suffering and pain. She suggested that over the next several months—with the help of the RAC, researchers in experimental therapeutics, and the broader community—NIH will need to develop a sensible policy that combines compassion with scientifically sound judgment.

Another area close to the hearts of the NCI and the NCAB, Dr. Healy continued, relates to the issues of technology and fair pricing. She noted that Drs. Broder and Chabner have had many meetings with congressional members concerning these matters, which will continue to be part of the national debate over the costs of health care in light of the fact that the portion of the health care budget for pharmaceuticals and medical devices comprises approximately $60 billion. Dr. Healy summarized the widely held belief that, because NIH supports 50 percent of all medical research in the United States, including 90 percent of all basic biomedical research, taxpayers have already heavily invested in experimental therapeutics and should receive a return on that investment in the form of "fair pricing." She suggested that, philosophically, everyone associated with NIH agrees, pointing out that NIH has incorporated a fair pricing clause into its Cooperative Research and Development Agreements (CRADAs) as well as into royalty and licensing agreements.

Dr. Healy explained that prior to the Bayh-Dole legislation of 1980, licenses and patents based on funded research had to be presented for NIH review. The 1980 legislation delegated patenting and licensing authority for Government-sponsored research to the funded institutions; in the case of NIH, this accounts for 85 percent of the research investment. Until recently, fair pricing issues affecting NIH focused on intramural laboratory activities related to agents such as AZT, ddI, taxol, and other drugs, many developed within the National Cancer Institute. Now, Dr. Healy stated, there is concern about the kinds of relationships that are being established between funded institutions and private companies—for example, a relationship in which Sandoz, at a cost of $30 million a year, has first refusal on all research produced by the Scripps Institute, which receives roughly $110 million a year from NIH.

Dr. Healy noted that Congressman Wyden expressed concern about this arrangement during the recent NIH reauthorization hearings, particularly because of the involvement of a foreign company. Dr. Healy suggested that in addition to the Congress, the universities, the pharmaceutical industry, and the public are likely to "weigh in" on this issue because of its relationship to the broader issue of health care costs. She urged the NCAB to stay informed and provide advice on this issue, noting that in December the Advisory Committee to the NIH Director spent most of its meeting discussing the issue of drug pricing. She stated that during that meeting it was made clear that the NIH should not get involved in regulatory matters

because it lacks the necessary expertise in economics and marketing and does not have access to proprietary information.

Dr. Healy called the attention of the Board to recently proposed legislation (S.1/H.R.4) that would aggregate within the Office of AIDS Research all NIH AIDS-related research programs across all of the Institutes; this represents expenditures of close to $900 million, of which about half is allocated to the National Institute on Allergy and Infectious Diseases (NIAID) and a significant portion is allocated to NCI. The Office of AIDS Research would have bypass budget authority and a mandate to develop a strategic plan. While confirming that the Department supports this legislation and that the Institutes are committed to making the transition work, Dr. Healy described the proposal as "a new way of doing business" for NIH.

Dr. Healy observed that many of the policy concerns that will profoundly affect NIH today and tomorrow are issues that have arisen externally. She stated that, historically, the role of NIH has been reactive rather than proactive; the structure of NIH as well as its growth have been determined by external forces, some that have been welcomed and some that have been met with resistance. An example, Dr. Healy noted, is the Human Genome Project, a project created from outside NIH, but which is now one of NIH's most important efforts.

Dr. Healy said that while NIH is never going to be, nor should it be, immune to directives from outside, including authorizing legislation, the purpose of the strategic plan that has been under development for the past 18 months is to define NIH—its mission, its objectives, and its priorities—in order to become more proactively involved in making it a better and stronger institution. She announced that final editorial work on the plan is underway; in its areas of emphasis, she added, the plan reflects the input of NIH Institute Directors and the scientific community. The section on critical sciences and technologies—including cell and molecular biology, the Human Genome Project, structural biology, computational biology, developmental biology, etc.—is listed first within the plan because it is seen within NIH as a major priority.

Dr. Healy explained that the strategic plan is not linked to the budget through the inclusion of specific dollar amounts. The priorities listed in the plan, however, represent NIH's budgetary priorities and, over the years, the way the budget is prepared has changed because of the strategic plan. Budgetary numbers are examined in terms of how much support is needed for critical areas of science, for training in these areas, and for critical health needs. The strategic plan, Dr. Healy stated, clearly points out imbalances and helps determine whether enough money is being put into fundamental science and into career development as opposed to training. Dr. Healy expressed her hope that the strategic plan, in final draft version, will be available for distribution within the next month.

In closing, Dr. Healy appealed to the NCAB to engage the issues she had presented and to use its influence in speaking out on the future of NIH.

Questions and Answers

Dr. Temin asked whether the legislation creating the Office on AIDS Research is a *fait accompli*. Dr. Healy noted that Dr. Temin had made a "noble effort" to affect the process and that his letter had been discussed at length during a hearing before Congressman Waxman's

committee, but she acknowledged that the legislation is probably irreversible, although the final vote has been delayed to study the comments that have been received from various groups. Asked by Dr. Temin whether the Board could comment on such legislation, Dr. Broder stated that the Board would not be prevented from expressing its professional opinion.

Dr. Salmon asked whether NIH will take a position on issues such as the arrangement between Sandoz and the Scripps Institute as regards the Institute's research allocation from NIH. Dr. Healy responded that little information is available so far other than what has appeared in the newspapers. She stated that lawyers for NIH have been asked to review the legal issues to determine whether NIH has any standing in the matter; at the present time, she added, it does not appear that NIH has much standing, but a letter on the matter has been received and must be responded to. At some point, she suggested, the issues will transcend NIH and the views of NIH leadership and advisory panels such as the NCAB will be sought; it is premature, she said, to speculate on what those views will be. Dr. Healy noted that the issue of an individual company involved in a joint relationship that is specific to a patent or license may differ from the issues raised when companies are given blanket, "up front" right of refusal to research products.

Dr. Healy observed that NIH is an investment not just in the health of the Nation but also in its economic well-being, considering the fact that the biotechnology revolution has been fueled by NIH and small biotechnology businesses are expected to create millions of jobs in what promises to be a $50 billion industry. She stated that, all too often, NIH tends to get involved too late in these types of issues, but she stressed that more information and more input from the scientific community are needed before a position can be formulated.

V. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

House and Senate Membership Changes

Ms. Tisevich discussed the recent changes in House and Senate membership resulting from the November election. She commented that an increase in female and minority membership will affect the legislative agenda of the 103rd Congress.

Ms. Tisevich first related changes in membership of those committees that have jurisdiction over NCI's authorization and appropriations. On the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education, Senator Harkin from Iowa will continue to be chairman and Senator Specter of Pennsylvania will remain the ranking minority member. Senators Herbert Kohl of Wisconsin and Patty Murray of Washington, the only woman on the Appropriations Subcommittee, are the two newest Democratic members. Republican Senators Connie Mack of Florida and Christopher Bond of Missouri are also new members. Ms. Tisevich pointed out that Senator Mack is a long-time supporter of cancer research, prevention, and information dissemination activities due to his personal and familial experiences with cancer.

On House appropriations committees, Ms. Tisevich reported that Mr. William Natcher is now chairman of the full Appropriations Committee and will continue in the role of subcommittee chairman. Democratic Representatives Nancy Pelosi of California, Nita Lowey and José Serrano of New York, and Rosa DeLauro of Connecticut will replace Democratic Representatives Roybal, Early, and Mrazek. Representative John Porter of Illinois is the new ranking minority member. Two new minority members of the subcommittee are Helen Bentley of Maryland and newly elected Henry Bonilla of Texas. Ms. Tisevich added that the number of women on this subcommittee has increased from zero to four. She stated that Representatives Pelosi, Lowey, and DeLauro have all been active supporters of women's health research. Ms. Tisevich related that House Appropriations Subcommittee hearings may be held in April.

Regarding authorizing committees, Ms. Tisevich explained that Senator Nancy Kassebaum is the new ranking minority member on the Senate Committee on Labor and Human Resources; she has a strong interest in orphan drug development and pediatric AIDS. Although he remains a member of this committee, Senator Hatch relinquished his ranking position on this subcommittee to assume the ranking seat on the Senate Judiciary Committee. Democratic Senator Wofford of Pennsylvania replaced Senator Brock Adams, and Republican Senator Gregg of New Hampshire replaced Senator Cochran of Mississippi.

Representative Henry Waxman of California remains the chairman of the Committee on Energy and Commerce's Subcommittee on Health and the Environment. The new ranking minority member is Thomas Bliley of Virginia, replacing Representative William Dannemyer of California. Ms. Tisevich remarked that there are 11 new members on this subcommittee, which has no female members.

NIH Revitalization Amendment of 1993

Ms. Tisevich reminded the Board that President Bush vetoed the NIH reauthorization bill. She explained that on January 21, 1993, Senator Kennedy introduced S.1, the NIH Revitalization Amendments of 1993. Representative Waxman introduced the House version of the bill (H.R.4) on January 5, 1993. Ms. Tisevich summarized portions of the bill that affect the NCI. The bill authorizes appropriations of $2.2 billion for the NCI for FY 1994. She explained that, in the past, the NCI has received one authorization for research and one for cancer control, which now would be combined for one level of authorized appropriations.

Ms. Tisevich outlined the proposed authorizations of appropriations: $225 million for basic research in breast cancer of a total $325 million increase for breast cancer; $75 million for other women's cancers; and $72 million for prostate cancer. Dr. Becker asked whether the $225 million authorization for basic research is for basic research alone or basic research in which the term "breast cancer" is used. Ms. Tisevich explained that the Congress intends for $325 million more to be spent on breast cancer research, but it has a particular interest in basic research that will enhance breast cancer knowledge. She reported that $472 million would be authorized for disease-specific research, in addition to the $2.2 billion authorization.

Ms. Tisevich explained that the NCI had a separate dollar authorization for cancer control in the past, but the NIH reauthorization bills would require that prevention and control

be funded at 10 percent of the full appropriation level. To attain this earmark incrementally, Congress would authorize the NCI to fund cancer control at 75 percent ($193 million) of the bypass request for FY 1994 ($257.5 million).

An extensive section was added to the bill directing the NCI to develop an expanded program on breast, cervical, and ovarian cancers to be coordinated across the NIH with other ICDs. The NCI must develop a research plan; submit it to the President's Cancer Panel, the Secretary of Health and Human Services, and the Director of the NIH; and submit copies of the plan to the House and Senate authorizing committees. The first plan is due on May 1, 1993, and should be updated and revised periodically. The bill directs the NCI to provide a summary of the implementation and progress of the plan for the NIH Director's biennial report. Also, the NCI must fund six SPOREs in breast cancer. The Senate and House versions of the NIH Revitalization Amendment include requirements for prostate cancer similar to those proposed for breast and other women's cancers.

As Dr. Healy mentioned in her talk to the Board, Ms. Tisevich stated that there are some new provisions related to the NIH Office of AIDS Research in terms of resource allocation and funding decisions. The intent of the new provisions is to improve the coordination of AIDS research at the NIH.

Recent Hearings

On February 3, 1993, Representative Waxman held a hearing on the NIH reauthorization bill at which Secretary Shalala testified in support of the bill, including the AIDS provisions. Secretary Shalala did, however, point out areas in which the bill micromanages the NIH. The Secretary also indicated her hope that the Congress will work to remedy any problems that arise out of the new AIDS provisions. Ms. Tisevich reported that the House should mark up the bill sometime in February.

Representatives Wyden and Waxman and Senator Pryor are focusing on drug pricing. On January 25, 1993, Representative Wyden held a hearing on drug pricing at which Dr. Bruce Chabner testified regarding the Government's role in the development of taxol. Ms. Tisevich announced that a hearing on the development of AIDS drugs is scheduled for February 24, 1993, before Senator Pryor. She added that Dr. Adamson discussed the risk of brain cancer resulting from the use of cellular phones before Representative Markey's Subcommittee on Telecommunications and Finance last week.

Ms. Tisevich directed Board members to the legislative update included in their meeting packages for further information on recent activities. She noted that several bills that were not enacted during the 102nd Congress have been reintroduced. Ms. Tisevich reminded Board members that her office can provide copies of any bills or report language to them.

Questions and Answers

Dr. Bettinghaus asked when FY 1994 begins. Ms. Tisevich answered that FY 1994 begins on October 1, 1993. Dr. Bettinghaus questioned whether the bypass budget due in May of 1993 relates to FY 1994. Ms. Tisevich replied that that bypass budget is for FY 1995.

Motion for Tobacco Tax

Dr. Salmon explained that he drafted a resolution on a proposed tobacco tax, which was introduced and seconded by Dr. Bettinghaus at the previous NCAB meeting. This resolution, he commented, was distributed to the Board and comments were received from eight members. Dr. Salmon stated that, if passed, this resolution would be forwarded to the present administration and the Congress. He then read the resolution:

Whereas, there is the overwhelming evidence that the use of tobacco products causes cancer; and

Whereas the use of tobacco products causes over 300,000 cancer deaths annually in the United States of America and numerous deaths from heart and lung disease; and

Whereas the use of tobacco products in children and adolescents has steadily increased in recent years; and

Whereas smoking in women and minorities has increased, and the lung cancer death rate in women has doubled since 1970; and

Whereas public education alone appears to be inadequate by itself to correct the serious health problem; and

Whereas the health cost to our nation of the use of tobacco-related products is in the range of $50 billion annually, the National Cancer Advisory Board recommends the following actions:

That the U.S. Congress introduce and pass, and the President sign, legislation implementing a tax that results in a major increase in the cost of tobacco products;

That the tax be at least $2.00 per pack of 20 cigarettes, and that similar high taxes be added on a proportionate basis to the cost of cigars and of smokeless tobacco packages, inasmuch as all tobacco products cause cancer; and

That this new tobacco tax be linked to a consumer price index in such a fashion that the tax is increased whenever the consumer price index increases.

We additionally recommend that the proceeds from this new tax be equally split to support two important national priorities: (1) the cancer research program of the National Cancer Institute, including the NCI's ASSIST program to help prevent smoking and to help tobacco users rid themselves of their tobacco addiction; and (2) deficit reduction.

In making these recommendations the National Cancer Advisory Board takes recognition of the fact that the introduction of a similar taxation strategy by several other countries, as well as by several individual States in the United States of America, has resulted in reduction in the use of tobacco products in those countries and States. Decreases in tobacco use are directly associated with reductions in the incidence of some of the most frequent and lethal malignant tumors, such as lung cancer. Moreover, an increase in the cost of tobacco products as a result of this tax would be the most effective way of reducing tobacco use by children and adolescents, by the economically disadvantaged groups in our society, and by minority or underserved populations which have proved so difficult to reach or engage in educational endeavors.

The poor, as well as members of ethnic and racial minorities, at present suffer from a higher incidence of tobacco-related cancers, such as lung cancer, head

and neck, and oral cancers, than the general population and, therefore, disproportionately suffer from the tragic personal consequences of these usually fatal forms of cancer.

We recognize that this recommendation goes far beyond the National Cancer Advisory Board's prior recommendations with respect to the dangers of tobacco, and is made with the recognition that such strong action is essential if the wastage of our nation's people due to tobacco-related illness is to be reduced and eventually eliminated.

Discussion

Dr. Calabresi asked the Board if they would like to discuss the resolution at that time or during the discussion of new business on the following day. Dr. Bettinghaus commented that the resolution had been distributed to members several weeks prior to this meeting and members, therefore, had had ample time to familiarize themselves with its content.

Ms. Mayer explained that cigarettes became very expensive in Massachusetts after tax increases were imposed. Distributors are now packaging cigarettes singly or in groups of five in order to make them more affordable for adolescents. Ms. Mayer suggested that these small packs of less than 20 cigarettes should be addressed in the first paragraph of the resolution. Dr. Salmon answered that the language indicates how a package of 20 cigarettes would be taxed and does not imply that a smaller package would not be taxed. Ms. Mayer stressed that she would like the language to specifically address this marketing approach. Dr. Salmon suggested adding the words: "On a proportionate basis the cost of individual cigarettes, cigars, and smokeless tobacco," to which Ms. Mayer agreed.

Dr. Wilson related that the State of California has a cigarette tax of $.24 per package, which was originally designated for educational purposes. He expressed concern that a Federal tax would affect the States' ability to generate their own revenue through a State tax. Dr. Salmon answered that other countries with lower per capita income than the United States have higher taxes ($3.00) than this proposed tax.

Mr. Alan Davis of the American Cancer Society reported that there is a national campaign urging States to increase their excise taxes by as much as $1.00 per pack, in addition to a Federal tax of $2.00. He added that there is no self-imposed limit on the amount of tax on cigarettes. With the combined State and Federal tax amount of $3.00, he said, the United States would rank at the mid-level of taxing among industrialized nations. Compared with other industrialized nations, the United States taxes less on cigarettes than any other country. Mr. Davis added that taxes comprised 49 percent of the price of a pack of cigarettes in 1965, compared with 24 percent today. Prices have been increased by the tobacco companies, thus increasing profits.

Dr. Bragg commented that the purpose of this resolution is to blunt tobacco sales and not necessarily to generate money for the NCI. Dr. Salmon stated that the motion has two objectives, the more important being the reduction of tobacco use. Dr. Bragg asked about the results of tobacco taxation in countries that have imposed higher taxes than the United States and whether the National Heart, Lung, and Blood Institute (NHLBI) is aware of this resolution. Mrs. Bynum commented that it is not necessary to involve another Institute in this activity

because the resolution is based on Board members' individual feelings as private citizens. The motion can be shared, however, at the National Advisory Meeting of the Heart, Lung, and Blood Council. Dr. Bragg expressed his desire to include the NHLBI in order to gain stronger political ground. Dr. Calabresi stated that the NHLBI would be notified and asked to participate.

Dr. Sigal expressed her support of the resolution. She suggested that the proceeds of the tax be used to benefit health care, which affects both deficit reduction and health promotion. Dr. Sigal also suggested that the NCI request 50 percent of the proceeds, recognizing that perhaps 20 percent will be given. She stated that it would probably be politically popular to designate proceeds to health care, and asked how the process of the resolution will be handled, in anticipation of the tobacco industry's disapproval of the resolution.

Dr. Bettinghaus stated that it is appropriate for individual boards such as the NCAB, which is a health-oriented organization, to propose particular use of such taxes. He added that the Congress, however, would probably object to earmarking funds. Citing California as an example, Dr. Bettinghaus pointed out that tobacco consumption generally decreases when a significant tax is added and does not easily increase again. This resolution, he said, would suggest that the NCI sees a need for additional funding for cancer research and is proposing a means to obtain it. It is important to remember, Dr. Bettinghaus added, that whether or not Congress decided to appropriate the proceeds to another area, cigarette consumption would decrease and a significant design would have been created.

Regarding Dr. Sigal's comment, Dr. Salmon stated that the resolution should be forwarded to the Congress and the new administration on behalf of the Board. The rest of the process, he said, would depend on voluntary organizations, such as the American Cancer Society. Dr. Salmon added that the health costs of tobacco are estimated at approximately $7.00 per pack for all diseases. Thus, the tax is a small attempt at restoring the health care budget. Dr. Sigal agreed with Dr. Salmon, but noted that she would like to add a sentence to the resolution addressing deficit reduction and health care, especially long- and short-term reduction of health care costs.

Mr. Davis indicated that he was speaking as the chairman of the Coalition on Smoking and Health, an organization of the American Cancer Society, the American Heart Association, and the American Lung Association. He stressed that the NCAB's support of the Coalition on Smoking and Health's national tobacco excise campaign would be extremely beneficial to the cause of reducing tobacco use. Mr. Davis explained that the Coalition is currently working with the Congress to develop interest in this campaign. He reported that some public health economists have estimated that the Federal tax of $2.00 would generate between $30 and $35 billion a year in revenue. A $1.00 tax on the State level would generate about $20 billion. Mr. Davis noted that it would be prudent not to earmark the revenue on the Federal level, but that earmarking on the State level, such as in California and Massachusetts, has proven effective.

Dr. Wilson suggested that the resolution specifically address the States, because pricing alone in the absence of education cannot reduce tobacco consumption. He suggested that the

Board could increase the power of the resolution by suggesting that the tobacco tax be levied by the States and used, at least in part, for educational purposes. Dr. Calabresi contended that the NCI ASSIST program involves education and local State health departments. Dr. Wilson added that the California tax made this program more effective. Dr. Salmon agreed that the ASSIST program specifically focuses on States providing education, but maintained that States may still pass their own additional legislation with earmarking.

Regarding Dr. Sigal's suggestion, Dr. Salmon suggested adding the phrase "and because successful cancer research can reduce health care costs" to the part of the resolution that reads "whereas the health cost to our nation of the use of tobacco-related products is in the range of $50 billion annually . . . ." Dr. Salmon stated that he has no objection to involving the National Heart, Lung, and Blood Institute on the resolution, but he emphasized that a separate resolution from that Institute would be more powerful. Dr. Calabresi remarked that the NHLBI would probably issue a resolution endorsing the NCAB's statement and that the NCAB should continue taking the leadership role on this resolution.

The Board unanimously approved this motion.

VI. CANCER VACCINES—DR. THIERRY BOON

Dr. Chabner invited the Board to a concert, performed by a patient, in the clinical center at 7:30 p.m on the 14th floor.

Dr. Chabner remarked that Dr. Thierry Boon's presentation about his studies of tumor-specific antigens in melanoma at the General Motors Awards assembly in 1991 represented a remarkable revelation in science. He explained that scientists have tried to capitalize clinically on the fact that the immune system recognizes tumors by developing vaccines based on the use of whole cells or fragments of cells. Scientists had not, however, identified a specific antigen to use for vaccination. Dr. Chabner reported that Dr. Boon and his colleagues at the Ludwig Institute in Belgium have identified a series of antigens, first in animals and now in human tumors, which could lead to new possibilities in cancer vaccination. He then introduced Dr. Boon.

Dr. Boon explained that for many years, scientists have been studying antigens that are present on cancer cells, particularly antigens recognized by cytolytic T-lymphocytes (CTLs), lymphocytes that destroy cells when they recognize an antigen on them. Scientists have attempted to identify genes that target antigens and to understand the mechanistic changes in old genes that bring about new antigens recognized by cytolytic T-lymphocytes.

Dr. Boon described the difference between the cellular materials recognized by antibodies and cytolytic T-lymphocytes. Antibodies recognize only those molecules that are anchored in the cell membrane and presented on the outside of the cell. When viruses invade cells, he explained, the cells produce proteins that are not only expressed on the surface, but often remain strictly inside the cells where antibodies cannot recognize them. The cells digest a fraction of these proteins and generate small peptides that are 9 or 10 amino acids long,

which move to the endoplasmic reticulum, where they bind to specialized molecules called major histocompatibility complex (MHC) molecules in humans, HLA molecules, and class I molecules. The molecules travel to the surface of the cells and present the peptides to the CTL, which has a specialized receptor. Dr. Boon noted that HLA molecules vary from person to person and affect one's reactivity to some viruses. He presented a slide of the HLA molecule and pointed out its specialized groove in which the peptide can bind.

In the course of identifying genes that code for new antigens recognized on mouse tumors, Dr. Boon said his group found that any genes can be expressed in any cells and, when mutated, lead to the generation of new antigens by two basic mechanisms. He explained the first mechanism, in which the gene is expressed in all cells but the peptide generated from the protein cannot bind to MHC molecules; not all peptides, he noted, can bind. The mutation transforms an amino acid into a peptide, which can bind to an MHC molecule. Thus, a new antigen is presented by CTL that is potentially tumor specific. Dr. Boon added that there is a possibility that mutated oncogenes generate new antigens in this manner.

Dr. Boon described another mutational mechanism, in which the peptide encoded by the normal gene is able to bind to an MHC molecule, but, because of natural tolerance, the CTLs that recognize it are eliminated. The mutation then changes the shape of the peptide, enabling a new set of CTLs to recognize it.

Dr. Boon explained that the second major mechanism is gene activation. If a gene is silent in normal cells but is activated in a tumor, it will produce a protein and a peptide, which may possibly bind to an HLA molecule and be recognized. Dr. Boon related that his group has identified a tumor rejection antigen that is specific for a mouse blastocytoma. This antigen is not present on normal cells because they express little or none of that gene.

Dr. Boon described efforts to isolate CTL that can act upon human tumors. He explained that much research on human melanoma has been conducted because it is relatively easy to grow cell lines *in vitro* from melanoma tumors. Dr. Boon described the following procedure to isolate (CTL) lymphocytes that act upon tumor cells: obtain blood from the patient; isolate the lymphocytes; perform a mixed lymphocyte tumor cell culture; perform autologous stimulation (the patient's irradiated tumor cells are added to the lymphocytes); and incubate the lymphocytes with the tumor cells to obtain CTL with the ability to lyse the tumor cells. With the proper lymphocytes that result from this process, Dr. Boon stated, he mixes a single lymphocyte with irradiated tumor cells. If this single cell is stimulated, it recognizes an antigen on the tumor cells and proliferates, resulting in a large population of cytolytic T-lymphocytes that will recognize the same antigen.

Dr. Boon related an experiment that allows researchers to assess the number of different antigens recognized by CTL. CTL clones derived from different lymphocytes were isolated in a patient called MZ2. Dr. Boon explained that he and his colleagues mix a few million CTLs from one clone with a few million cells of an autologous tumor. Normally, he explained, the CTLs destroy the tumor cells but, usually, about one tumor cell in one million survives because it loses the antigen recognized by CTL.

Dr. Boon presented data on what he calls the MZ2-mel cell line—two CTL clones directed against the melanoma from patient MZ2. He explained that the CTLs' ability to destroy tumor cells is measured by a lytic assay with chromium, a procedure in which tumor cells are labeled with chromium and if recognized by the CTL, will explode and release their chromium. Dr. Boon stated that these particular CTLs are extremely active, able to destroy more than 50 percent of cells they are given within 4 hours, with effector-to-target ratios as low as 1:1. This, he pointed out, is good activity in such an *in vitro* test. Dr. Boon explained that the CTLs are remarkably specific and will not lyse an NK or LAC target called K562, autologous B cells of the patients immortalized with EBV, or the fibroblasts of the patient.

Dr. Boon reported that when a clone resistant to a CTL is isolated, he submits it to lysis by other members of the panel of cells. If it is lysed, he said, it becomes obvious that these CTLs recognize another antigen. Dr. Boon explained that the panel of CTLs for this melanoma recognized at least six different antigens, resulting in antigen loss barriers for several cells. Dr. Boon said that his team then decided to work to identify the antigen they called E and the gene that codes for antigen E. DNA was obtained from the initial melanoma cell that was recognized by CTL, called antigen MZ2-E. Dr. Boon explained that he attempted to transfect the DNA to reintroduce it in the antigen loss variant, antigen E, that was resistant to the CTL. Transfectants that express the antigen are detected by their ability to stimulate tumor necrosis factor (TNF) released by the CTL. Once he obtains the transfectants, Dr. Boon said, he builds a cosmid library from the genomic DNA, repeats the entire process, and uses the cos sequences from the special vector to retrieve the transfected gene. Thus, Dr. Boon noted, he and his colleagues isolated the first gene from a melanoma tumor about a 1-1/2 years ago.

Dr. Boon presented a slide of a gene with two small exons and one large exon on which the open reading frame was located. When he and his colleagues examined the gene banks, they found that it was unrelated to any known gene. They also found that this gene in the tumor did not carry a point mutation that differentiated it from the gene found in normal cells and that, therefore, the antigen originated through the gene activation mechanism. Dr. Boon said that when he and his colleagues compared the genomic sequence of the cDNA that they had isolated from the tumor, they found not one, but three messenger RNAs corresponding to the gene. All genes that they had previously called melanoma antigen (MAGE) were then renamed MAGE-1, one of a family of 11 different genes that are 80 to 95 percent related, have essentially the same structure, and are located on chromosome X. Of these 11 genes, only MAGE-1 codes for the E antigen.

Dr. Boon explained that he and his group looked for expression of the gene by preliminary chain reaction (PCR) amplification and screening of all PCR products with probes specific for either MAGE-1, MAGE-2, or MAGE-3, the first three genes of the sequence. The initial tumor expressed all three genes. The E antigen loss variant expressed MAGE-2 and MAGE-3, but not MAGE-1. Dr. Boon pointed out that they knew that the expression of MAGE genes was not a tissue culture artifact, because a preserved metastasis from the same patient also expressed the three genes. Negative expression of the three genes in a lymphocyte from this patient and normal tissue samples from other persons indicated that these genes might be tumor specific. Other melanoma tumors either: 1) did not express MAGE-1, MAGE-2, or MAGE-3; 2) expressed MAGE-2 and MAGE-3, but not MAGE-1 (the majority);

or 3) expressed MAGE-1, MAGE-2, and MAGE-3. Lung and thyroid tumors also expressed MAGE-2 and MAGE-3, and, sometimes, MAGE-1.

Dr. Boon stated that his group recently carefully reexamined the expression of MAGE-1, using the PCR approach. They found that all normal cell samples were negative for MAGE-1 expression, except testes cells, which were positive for all MAGE genes at a level of approximately 30 percent. Looking at a number of different tumors and tumor samples, about 40 percent of melanoma tumors, 20 percent of breast cancer cells, and 30 percent of nonsmall-cell lung cancer cells are positive for MAGE genes. Dr. Boon stated that although not all tumors express enough protein to have sufficient peptide to be recognized by CTL, he predicted that two-thirds of tumors found positive by PCR will have enough peptide.

Dr. Boon explained that the antigen is a combination of HLA molecule and a peptide. HLA typing of the initial patient and examination of the number of melanomas that share some HLA with the patient will reveal the identity of the presenting HLA molecule. All melanomas that were positive for MAGE-1 and shared HLA-1 with the patient were recognized by the anti-E CTL, either by TNF release or lysis assays. A number of melanomas that were positive for MAGE-1, but that shared other HLA with the initial patients, were all negative. Thus, HLA-A1 was the presenting molecule. Dr. Boon recounted that approximately 25 percent of Caucasians express HLA-A1, while those of African origin express about 17 percent. He added that HLA-A1 and the MAGE-1 gene are recognized in mouse cells.

To isolate the MAGE-1 peptide, which Dr. Boon said he found to be a highly efficient nonapeptide, he cut the gene into small pieces to find the regions that could transfer expression of the antigen and encode the antigenic peptide. Dr. Boon explained that if cells of the A1 type that do not express the antigen were incubated in the presence of this peptide, the result was good lysis. If the last and first amino acids were removed, nothing happened, which indicated the presence of a minimal peptide. These peptide concentrations were very effective in the nanomolar range.

Dr. Boon discussed three conclusions drawn from this experiment. First, since the MAGE-1 gene is tumor specific, it is believed to be expressed in early embryos and only in the testes in adult tissue. Dr. Boon noted that the MAGE-1 gene is clearly specific enough for use in immunotherapy. However, he described a CTL from a lung tumor in which the gene seeking the antigen was expressed on every normal cell and was, therefore, useless.

Dr. Boon stated that it is necessary to evaluate whether the expression of MAGE-1 in the testes poses some risk in the immunization of patients. Since the testes express almost every gene, Dr. Boon explained, he does not think the expression will pose a risk. He noted that his group will also be able to determine whether there will be a side effect on the testes in mice by immunizing them against equivalent genes in male mice and examining their health and performance.

Dr. Boon's second conclusion is that, in addition to oncogenes and antioncogenes identified in the past 10 years, a new set of genes will be identified immunologically. His group has identified the gene coding for mouse antigen, and there is evidence that the mouse gene called P1A is involved in tumor transformation. Since this gene is not homologous to

any known gene, Dr. Boon said he has great interest in finding the human equivalent. He does not believe that MAGE promotes tumor formation, because it tends to halt growth when transfected. Dr. Boon shared a preliminary finding that only 2 of 17 MAGE-1 expressions in melanoma are positive in primary lesions, but 50 percent are positive in metastasis. If true, this result would suggest that MAGE-1 is involved in the metastatic process and, perhaps, patients could be immunized with MAGE-1 negative tumors, which contain a few MAGE-1 positive cells. Dr. Boon cautioned that this result could be biased by the fact that primary tumor samples received may not all contain true tumor cells.

Dr. Boon's third conclusion is related to immunotherapy. He explained that if the target antigen and its gene are unknown, it is necessary to either: 1) immunize one patient with cells from another patient without knowing whether he or she expresses the antigen on this tumor; or 2) manipulate the tumor cells of a patient and reinfuse them into that patient with the hope of immunizing, which is costly and difficult to reproduce, since no two tumors or tumor samples are exactly alike. Conversely, if the antigen is known, it is easier to evaluate its efficacy. For example, a melanoma patient with a primary tumor and possible metastasis would be typed for HLA. If the patient carried HLA-A1, the surgeon would be asked to retain a small tumor fragment to establish whether the gene is expressed on the tumor by PCR. Expression occurs in about 40 percent of melanomas. Since about 25 percent of Caucasian patients carry HLA-A1, only 10 percent of all patients should be eligible.

Dr. Boon explained that if the gene is expressed on the tumor, it is known that the patient carries the antigen, he or she can benefit from immunization, cells that express the antigen are available for immunization, the immunogen can be manipulated, and the patient can be evaluated clinically and for increased frequency of CTLs directed against the antigen. He stressed that a sound strategy would be to immunize small numbers of patients until there is a way to regularly induce CTL in them. After this is accomplished, Dr. Boon suggested, it can be determined whether patients with more CTL enjoy a better clinical evolution.

Dr. Boon reviewed several possible modalities of immunization. It is possible to immunize with cells that express antigen E after they have been killed by irradiation, but, Dr. Boon cautioned, it is likely that a strong antiallogeneic response would suppress the anti-E reaction. Possibly, he suggested, human cells that do not express HLA genes can be transfected with HLA-A1 and MAGE-1 to avoid most of the antiallogeneic effect. It is also possible to transfect these cells with various interleukin genes or additional molecules, such as the B7 molecules, to augment their immunogenicity. Another mode of immunization would be to treat patients with a peptide combined with the appropriate adjuvant, which could lead to the generation of CTL through presentation of the peptide by macrophages and dendritic cells. It is also possible to collect macrophages and dendritic cells from patients, incubate them *in vitro* with peptide or protein, and reinfuse them into the patient. These macrophages could also be infected with recombinant retroviruses carrying the MAGE-1 gene. The macrophage would express the antigen and be reinfused. Another possibility is to inject patients with recombinant BCG bacteria carrying MAGE-1. There is also an approach using adoptive transfer of CTL.

Dr. Boon stated that there are technical limitations involved in this work and that short-term success is doubtful. There is no good way, he said, to measure antitumor CTL in patients

or to evaluate the efficacy of immunization. Also, as Dr. Boon had noted earlier, only about 10 percent of melanoma patients would be eligible for immunization, and this number, he said, would be reduced to 5 percent in a clinical pilot study because of age, prognosis, compliance, and other issues. Dr. Boon pointed out that it will be necessary to investigate whether an attack against a single antigen will be capable of destroying tumor cells *in vivo*. There is also the risk of antigen loss variance. Dr. Boon stated that many of these problems can be overcome if more genes and antigens are identified.

In conclusion of his presentation, Dr. Boon discussed positive new findings. The MAGE-1 gene, he said, not only makes a peptide that binds to HLA-A1, but a peptide that binds to an HLA-C molecule as well. Of the HLA class I molecules, the A, B, and C molecules are important for CTLs. There is, therefore, an AC molecule that can present an antigen actively encoded by MAGE-1, and this antigen is recognized by a different lymphocyte than the first anti-E lymphocyte.

Dr. Boon explained that his group has been interested in several antigens recognized by CTL on many A2 melanomas. The group has tried to identify the antigen of CTL that recognizes many melanomas by making cDNA libraries that express in cos cells with a human HLA gene. They examined whether cos cells transfected with these cDNA are capable of stimulating the CTL recognizing these antigens. Two months prior to this meeting, Dr. Boon said, he and his colleagues identified a cDNA that could transfer good expression of the antigen by cos cells when transfected with HLA-2. They sequenced this DNA and found that it targets tyrosinase, an enzyme responsible for the synthesis of melanin in melanocytes and melanoma. Dr. Boon stated that this gene will not be entirely specific for melanoma, but will be present and expressed on melanocytes. He cautioned that there could be dangerous side effects of an untyped tyrosinase immunization, because there are also melanocytes in the retina. Dr. Boon added that his group will use mouse cells to determine the side effects of antityrosinase immunization.

Dr. Boon predicted better prospects for clinical pilot studies with these new genes and antigens. For example, 10 percent of melanoma patients could be treated for the E antigen due to the presence of A1s and MAGE-1. Dr. Boon said he believes that HLA-C will be expressed in about an additional 10 percent of patients, therefore doubling the number eligible for MAGE-1 therapy. If tyrosinase is found to work in the A2 system, a large group of patients could be targeted, since HLA-A2 is the most frequent HLA and tyrosinase is expressed in a very large percentage of melanomas. The number of melanoma patients would, therefore, rise to about 50 percent, accounting for overlap. Dr. Boon expressed interest in immunotherapy for a small number of patients that would express all three antigens.

Dr. Boon concluded that there is much work to be done and there are many more genes to identify. He expressed hope that he can soon evaluate the dangers and benefits of vaccination against cancer antigens recognized by CTLs.

Questions and Answers

Dr. Becker congratulated Dr. Boon for his outstanding work and commented that massive immunotherapy against unknown antigens has been conducted unsuccessfully for

many years. He asked Dr. Boon whether the MAGE-1 gene is expressed as a surface antigen in breast tumors. Dr. Boon answered that little immunology has been conducted on the breast because it is extremely difficult to obtain breast tumor cell lines from patients; thus, there has been little indication. There has been evidence, however, of expression on lung tumor cells. Dr. Boon pointed out that not all MAGE-1 positive and A1 positive cell lines have been in melanoma, some have been in tumors of the colon and some in sarcoma.

Dr. Becker asked whether Dr. Boon has considered the problem of downregulation of tumor cells in immunotherapy and whether he has considered the use of cytokines or interferon to re-express antigens. Dr. Boon replied that he is more concerned about HLA downregulation or elimination than MAGE-1, because all tumors analyzed have expressed several antigens. If several antigens attack, some cells may delete one gene or another, but not all of them. Some cells, however, eliminate all their HLA. Dr. Boon explained that, based on his intuition, not fact, there is probably a solution to selecting a few HLA escape variants as a result of selective pressure. A Swedish colleague, he added, has hypothesized that certain NK cells specialize in recognizing cells that do not express HLA. Dr. Boon surmised that the purpose of the NK cells is to attack abnormal cells that have escaped.

It is possible to treat patients with interferon and other agents that would upgrade HLA, Dr. Boon continued. He added that this would also be a useful procedure for classes of tumors that express low HLA. Dr. Boon concluded that he is concerned about the possibility of ever finding a solution for tumors that are globally devoid of HLA as a result of previous immune pressure.

VII. COST OF HOME CARE FOR CANCER PATIENTS—DR. VINCENT MOR

Dr. Mor began his presentation by stating that the relevance of the cost of home care for cancer patients is that if patients' home care costs and treatment-associated burdens are too high, new treatments may not reach their intended target population. He mentioned that much has changed since he last appeared before the Board in 1983 to present results of the National Hospice Study, which compared the costs and quality of life experiences of patients with terminal cancer who had been serviced by hospice versus conventional oncological care. Since there are limited data available specifically on the study of the home care costs of cancer patients, Dr. Mor discussed the context of the issue.

Dr. Mor presented slides and reviewed health care delivery trends and issues related to the rising use of home care, decreasing hospital use over the past decade, increasing hospice use, and increasing home death. He pointed out that he would begin discussing data from the system-wide basis and move toward cancer-specific data. Dr. Mor said he would document the incidence and prevalence of home care use and associated costs, describe costs borne by family members, and propose an agenda for better understanding this issue.

Dr. Mor stated that it is crucial to understand that cancer care has been increasingly dehospitalized over the past decade. Memorial Sloan-Kettering Cancer Center instituted the first day hospital treatment center in 1984. Many day hospital treatment centers now exist that

provide extensive outpatient therapy, chemotherapy, and radiation therapy, as well as diagnostic and minor surgical procedures for patients. In Dr. Mor's randomized trial, he found that although there were no improvements in the quality of life of patients in the day hospital, there were substantial cost savings. Examining costs to family members who transported patients to treatment on an ongoing basis, there was no substantial increase in psychological burden. While all family members did lose a substantial amount of time at work, Dr. Mor noted that there was virtually no difference between hospitalized patients and patients who came and went for day treatment, suggesting that the burden is present regardless of whether the patient goes home at the end of the day or not.

Dr. Mor explained that the onset of diagnostic-related groups since 1983 has reduced the length of stay and drastically reduced the number of patient days associated with most chemotherapy sessions. In some areas, he continued, it is standard procedure to conduct chemotherapy on an outpatient basis, and third-party payers will not allow hospital admissions for this purpose.

In 1983 and 1984, Medicare and Medicaid opened up coverage for hospice under a home care model. Certified home health agencies were a catalyst for the provision of home care for cancer patients in the early 1980s. The agencies experienced an explosion at that time and the trend peaked in the mid-1980s. There has been a substantial increase in total charges in the Medicare home health care program.

Dr. Mor described another area of growth—hospital-based home health agencies. He presented a slide indicating that the number of persons served by hospital-based home health agencies tripled over the course of 6 or 7 years. There also was a substantial increase in total charges to the Medicare program between 1989 and 1990. Dr. Mor pointed out that growth has not been restricted to the Medicare program. He presented figures for Medicaid payments for selected medical services in fiscal years 1975 ($7 million) and 1986 ($1.3 billion). There has been a substantial increase in other services, including other therapies, supplies, consumables, and therapies delivered to Medicaid patients at home. Inpatient services have decreased by about 3 percent. Although it represents a substantial component of Medicaid costs, nursing home care also showed a relative (percentage) reduction.

Dr. Mor presented data from an American Association of Home Health Agencies survey on high-tech home care expenditures for infusion therapies. This market has been increasing dramatically in terms of total number of expenditures. CareMark, one of the largest providers of home care services, reports that approximately 15 million patients are receiving therapies. CareMark is approaching the 20 million mark in patients served and estimates continued linear growth over the next 4 years. Dr. Mor commented that CareMark has been successful in reaching out to these populations and serving complicated cases at home.

Dr. Mor stated that the use of hospices continues to grow dramatically. He explained that as of 1989, slightly less than 70,000 patients had been served under the Medicare program and Medicaid numbers are even higher. Dr. Eggers at the Health Care Financing Administration (HCFA) reported to Dr. Mor that these numbers have been rising over the past 3 years. The total number of hospices that are providing services to a large number of patients also is increasing, so that individual growth of specific agencies is also continuing.

Dr. Mor explained that one way to look at the implications of increased home care is to examine the proportion of patients with cancer who die at home. A 1979 figure provided by the National Center for Health Statistics suggested that 15 percent of cancer patients died at home. A paper by McMillan in the *Health Care Financing Review* suggests that the current figure is 22.4 percent for Medicare beneficiaries. Small retrospective studies estimate that approximately 40 percent of patients died at home in the late 1940s. During the 1950s and 1960s, the number dropped to about 10 or 11 percent and then began to increase. A study conducted in 1984 suggested that 18.5 percent of patients died at home. The National Mortality Followback Survey conducted in 1986 suggested that of those individuals whose primary cause of death was cancer, 26.1 percent died at home. The trend is that younger patients experience home death, largely because older patients are more likely to die in nursing homes. Data from 1986 reveal that of those who died at home, 20 percent received hospice services during the last year of their lives. The National Center for Health Statistics is repeating the National Mortality Followback Survey this year (1993).

Dr. Mor presented data from a study in Rhode Island investigating home care needs of cancer patients. The data concern patients with advanced or extended cancer who initiated chemotherapy and/or radiation therapy on an outpatient basis. Dr. Mor presented a list of formal services provided to patients in the past month; light housekeeping and meal preparation were highest on the list, while home chemotherapy was rarely provided. A small proportion of these people were receiving these types of care from certified agencies, while a substantial amount of care was provided by family members. Dr. Mor found this to be true for the elderly, mentally retarded, and other disabled populations.

Dr. Mor explained that, as part of this study on home care needs of cancer patients, patients completed diaries during a 2-week period. Participants were monitored for their diligence in maintaining their diaries. When data were collected, it was found that prescription medications composed the highest percentage of additional out-of-pocket expenses incurred during the 2-week period. Family personal care expenses, including babysitting, occurred rarely.

Dr. Mor presented data from the NCI Applied Research Branch that was matched with the SEER registry data on Medicare claims. The data, divided into quarterly intervals, represented women diagnosed with breast cancer who were Medicare beneficiaries at the time of diagnosis. Ten percent of women with breast cancer in the first quarter after diagnosis were shown to be using some form of certified home health agency that was reimbursed by Medicare. The proportion of people using this service, however, dropped substantially in later quarters, presumably associated with postsurgical care at home. Turning to patients diagnosed with colorectal cancer, Dr. Mor pointed out a higher proportion of use and then a decrease in use similar to that of breast cancer patients. The stage distribution in colorectal cancer is broad, with more regional and metastatic cases at the time of diagnosis than in breast cancer; therefore, early- and late-stage patients are averaged out. Percentage rates were different for lung cancer patients. The percentage did not decrease as much as with other types of cancer, because many lung cancer patients do not survive the first full year after diagnosis.

Dr. Mor discussed the overall distribution of the consumption of health care costs during the course of cancer in terms of stages: diagnostic era; initial era; and terminal era.

The diagnostic and initial eras generally include the month before diagnosis and 3 or 4 months thereafter when chemotherapeutic and/or adjuvant therapies are begun. Intervening treatments occur subsequently, such as Tamoxifen therapy for older women with breast cancer. Dr. Mor explained that recurrence and surgeries associated with recurrence occur during the intervening treatment time period.

Dr. Mor stated that there was a substantially higher proportion of people using home care in the SEER and Medicaid data than in the Rhode Island data. He explained that a point prevalence examination was used in the Rhode Island data. Dr. Mor commented that there clearly are more people using home care than are reflected in the self-reported or billing data. He said that he could not provide national estimates or absolute figures on home care costs and burdens, but it is clear that cancer care outside the hospital is increasing. Dr. Mor predicted that the rate of home care will accelerate as the nation moves toward health care reform, but it must be examined over a longer period of time in order to better estimate the probability of home care use.

Dr. Mor summarized that hospice is a major provider and has had a major influence on where U.S. cancer patients die. The length of stay of a hospice patient under Medicare has been relatively constant since the benefit began in 1984, suggesting that earlier identification of patients is not occurring, which the medical community feared. Most home care is currently provided by family members, and will probably be even more extensively provided by the family in the future. Dr. Mor concluded that it is necessary to study the factors that influence people's decisions to proceed with or stop treatment because of financial or treatment burdens.

Questions and Answers

Regarding the slide depicting a tripling of high-tech infusion costs, Dr. Salmon asked whether this figure represents inflation in home health care agency charges for treating those who normally would receive intravenous chemotherapy or represents more extensive use in patients. Dr. Mor stated that he did not have a definitive answer, but he understands the estimation to represent the provision of more extensive therapies over a longer period of time. He added that, for many years, there was no charge for the actual administration of care by nurses in the home, because the price of a visit was included in the charge for individual substances, therapies, equipment, etc.

Dr. Salmon commented that Dr. Mor's figures on home chemotherapy are a gross underestimate, because intravenous infusions at home rarely require intervention by a health care provider. Dr. Mor stated that Dr. Salmon made a good point because, currently, our ability to track this type of phenomenon is restricted to that which is billed.

Ms. Mayer commented that researchers have not been examining lost salary and associated factors, although she is familiar with Barbara Givens' book on the burden of family care. She asked Dr. Mor what future research will be necessary to examine burdens on the family, and what kind of interventions need to be addressed in this research. Ms. Mayer added that she would like to see some ideas or recommendations generated for future direction of research. Dr. Mor replied that there was a meeting focusing specifically on these topics in April 1992.

Dr. Yodaiken asked if the SEER data are broken down into geographic regions. Dr. Mor answered that the data are broken down by geographic regions and that there is substantial variation from region to region. Historically, there has been much more aggressive use of proprietary home health agencies and high-tech home care on the west coast.

Dr. Sigal asked specifically how home health care costs can be made more efficient and what the trend is for home health care. Dr. Mor answered that the issue of costs is complicated; for example, the actual charge to Medicare for an outpatient chemotherapy visit at a public hospital may or may not be lower than the cost of a home infusion visit by a nurse. There have been few cost accounting studies of outpatient settings to determine economic differences in costs.

Dr. Day suggested that Dr. Mor examine home versus center dialysis. Dr. Mor stated that the cost of home dialysis is indisputably lower than facility costs, even though there has been no growth in the price of facility dialysis during the past 10 to 15 years.

Dr. Calabresi then announced times and locations of the subcommittee meetings and reminded Board members that Mr. Christoferson would speak to the Board about new principles on ethics in the closed session. He then adjourned the morning session.

VIII. STANDARDS OF CONDUCT—MR. DONALD CHRISTOFERSON

Mr. Donald Christoferson explained to members of the Board that they are considered Federal employees on those days on which they serve and, therefore, are subject to Federal Standards of Conduct. If a Board meeting adjourns at noon, a Board member is still considered a Federal employee for the remainder of that day. Mr. Christoferson continued by noting that it would be inappropriate for Board members to lobby before Congress on days of Board meetings, unless they were doing so as private citizens. He suggested that members who wish to visit their congressional representatives do so on days when they are not conducting Board business. Mr. Christoferson stated that NCAB members may not serve as expert witnesses before a congressional committee, or in a Federal court case in which the United States is a party, on the same day that they serve as members of the Board. Mr. Christoferson requested that Board members who are asked to testify before a congressional committee on the day of an NCAB meeting discuss this with Mrs. Bynum so that other arrangements can be made. He stressed that when NCAB members attend Board meetings, they are Federal employees for the entire 24-hour day and may not represent any organization other than the Government. Mr. Christoferson added that Board members may not speak to NCI staff about their own institutions' grants, cooperative agreements, contracts, or applications on the same day the Board meets. By doing so, he explained, they would be representing their institutions and, therefore, not the Government. Mr. Christoferson requested that Board members who wish to discuss business concerning their institutions with staff during an NCAB visit should do so the following day after the NCAB meeting is over—that is, on a day they are not Federal employees.

Questions and Answers

To Dr. Wells' question concerning when the day actually starts and ends, Mr. Christoferson answered that the day starts at 12:01 a.m. and ends at midnight.

A Board member asked whether Board members are considered Federal employees the day before an NCAB meeting. Mr. Christoferson replied that Board members are not compensated for the day before the NCAB meeting; therefore, members would not be considered Federal employees on that day. Dr. Salmon mentioned that this issue is relevant in May because the meeting starts on a Tuesday. Mr. Christoferson pointed out that Board members may arrive on Monday and talk to NCI staff about the status of their grants or contracts.

Dr. Calabresi asked whether Wednesday would still count as an official meeting day if an NCAB meeting was slated for 3 days (e.g., Monday, Tuesday, and Wednesday) and was adjourned early on Tuesday. Mr. Christoferson answered that it would not, because members would not be paid for the day that they did not work. Mr. Christoferson confirmed Dr. Calabresi's statement that if a meeting was adjourned at 2:00 p.m. on a Tuesday, that Tuesday would be a meeting day until midnight.

Mr. Christoferson reminded Board members to sign the certification notes stating that they had reviewed material concerning Federal Standards of Conduct. Mrs. Bynum added that the certifications should be submitted to her or to Dr. Gray.

Mrs. Bynum reminded Dr. Calabresi to discuss Dr. Temin's resolution before closing the afternoon session to the public. Dr. Temin explained that an NIH Revitalization Amendment is currently being considered in Congress and has already passed in the Senate. He added that there was a House hearing last week concerning a change in the Office of AIDS Research. Dr. Temin expressed concern that there are several aspects of this amendment that could be damaging, especially to the NIAID and the NCI. He said that in a couple of years, one new body would be in control of all AIDS-related funding; the NCI, therefore, would be subservient to this new body. Dr. Temin explained that it is not very clear who would comprise this new body and how they would conduct it. Negotiations are underway in the House concerning this issue. Dr. Temin expressed his belief that a resolution is needed stating the NCAB's concern that whatever results from this amendment does not act negatively upon the way cancer and all other diseases are treated. He added that the thrust of the resolution is to encourage Congress to look not just at AIDS, but also at how changes could impact the NIH and the entire research structure. Dr. Temin said he feels it would be useful for the NCAB to send the resolution to the DHHS Secretary and to the Waxman and Kennedy committees in an attempt to persuade them to take a second look at the impact of this amendment. He then moved that the resolution as distributed to Board members be approved.

Dr. Broder stated that it is pertinent for the NCAB to advise Congress on this issue and told Board members that if they approve the resolution, he will forward it to the appropriate channels.

Dr. Calabresi asked if there were any more questions before voting. Dr. Salmon asked whether the resolution provides sufficient information. Dr. Temin answered affirmatively and added that because the amendment is very technical, there would not be enough time to study the language at this Board meeting. Dr. Salmon explained that he wanted support from Dr. Broder for passing this resolution. Dr. Broder stated that Dr. Temin had written an extremely effective and eloquent letter that was read at the committee hearing; this resolution, he said, codifies some of the concerns expressed in the letter. He then asked for Dr. Temin's permission to distribute his letter to all Board members, to which Dr. Temin agreed. Dr. Broder added that he would staple Dr. Temin's letter to the resolution, if approved, so that its full implications would be obvious to its readers.

Dr. Calabresi called for a vote on the resolution, which was approved unanimously. He then announced that the Cancer Centers Subcommittee had been rescheduled for 5:00 p.m. in room 8, rather than 6:00 p.m. There being no further announcements or comments, Dr. Calabresi closed the remainder of the afternoon session to the public.

IX. UPDATE ON "SUICIDE GENES"—DR. R. MICHAEL BLAESE

Dr. Alan Rabson provided a brief overview of the accomplishments of Dr. Michael Blaese, Deputy Chief of the Metabolism Branch of the Division of Cancer Biology, Diagnosis, and Centers. Dr. Blaese is a pediatrician and was born in Minnesota. He came to the NIH in 1966 as a clinical associate in the Metabolism Branch and is now the Deputy Branch Chief, working with Dr. Thomas Waldmann.

Dr. Blaese began his discussion by introducing the concept of using gene transfer to assist in the elimination of cancer. He indicated that direct gene transfer, if possible, would be the ideal approach to use to transfer a variety of genes into tumor cells. However, he stated that actually delivering genes to every cell is still a problem. Dr. Blaese explained that once genes are delivered to the cells, there are many options that can be used, including replacing tumor suppressive genes or adding toxic genes using toxins or drug sensitivity genes aimed at inducing specific apoptosis of tumors.

Dr. Blaese then proceeded, sequentially, to describe various ways of killing tumor cells. One possibility, he said, is to link toxin genes, like diphtheria toxin or other toxins, under the transcriptional control of either inducible promoters or tumor-specific promoters. The advantage of inducible promoters, Dr. Blaese mentioned, is that they can be inserted into the tumor cell genes and be turned on either at a specific site or a specific time. However, disadvantages of this form of therapy include toxin expression at inappropriate times and the incorporation of heavy metals. Dr. Blaese identified tumor-specific promoters as more successful at killing tumor cells; an example is alpha-fetoprotein, which could uncover target gene expression in hepatoma.

Another option, Dr. Blaese continued, is to use microbial genes that encode a benign gene product that can confer sensitivity to a relatively nontoxic drug, or to use a microbial gene that confers susceptibility to treatment with antimicrobials and antibiotics. Two

microbial genes that Dr. Blaese's laboratory has worked with are the thymidine kinase (TK) gene from Herpes simplex and the cytosine deaminase gene from either fungi, or more usually, from *E. coli*. The thymidine kinase gene from Herpes simplex kills virus cells by converting acyclovir or ganciclovir into their toxic phosphorylated derivatives. This mechanism of killing can be exploited to kill proliferating tumor cells. In contrast, cytosine deaminase converts the antifungal drug 5-fluorocytosine into 5-FU. Therefore, cytosine deaminase can be used to generate an intracellular toxin or chemotherapeutic agent to kill tumor cells.

Dr. Blaese then showed a slide of a mouse with two lumps of cancer, one being the wild type tumor, and the other being a tumor that had been transduced to express either the TK gene or the cytosine deaminase gene. By treating the mouse with the prodrug, the cancer that expresses the foreign gene can be effectively eliminated. While the tumor is eliminated, a potential problem with the method is that, theoretically, one would need to have the susceptibility gene in every tumor cell in order to eliminate it.

Dr. Blaese discussed an experiment to illustrate the bystander effect, whereby it is not necessary to have the suicide gene in every single tumor cell to accomplish killing in a majority of cells. In the experiment, tumor cells that were transduced with the TK gene in tissue culture were mixed at various proportions with wild type tumor in a test tube. Subcutaneous lumps of mixed cancer were established and treated with the prodrug. Dr. Blaese indicated that the results of the experiment showed that when there was 100 percent of the wild type tumor (with no suicide genes), all animals developed the tumor and failed the therapy. In another example, in which 100 percent of the tumor cells were bearing the TK gene, about 90 percent of the animals were cured by treatment with ganciclovir. Dr. Blaese found that the interesting point about this experiment was that when 50 percent of the tumor cells in a particular lump were of the wild type, over 90 percent of the animals were being cured, and that when 90 percent of the tumor cells were of the wild type, over 50 percent of the animals were cured. Dr. Blaese concluded that there must be a mechanism within the system that allows the killing of the whole tumor even though only a small fraction expresses the introduced gene. This is critically important, he noted, because it may never be possible to transfer a gene into every tumor cell within a lump of cancer.

Dr. Blaese then discussed a method used to try to exploit local gene delivery. The model system was localized malignancy of brain tumors in rats, specifically gliomas. The strategy of the experiment was to stereotactically inject the gene for susceptibility—herpes TK in this instance—into a tumor. One problem with this approach, Dr. Blaese noted, is that it is not possible to deliver enough of a retrovirus to effectively deliver the gene by itself. In addition, retroviruses only integrate their genes into cells that are actively synthesizing DNA; if virus is injected at one time, only a small fraction of cells that are at the point of active DNA synthesis in the cell cycle will be hit.

The strategy developed to address these problems was to inject fibroblasts that produce the retrovirus vector locally into the tumor. Dr. Blaese stated that the fibroblasts could produce the retrovirus vectors that would transfer the gene into a tumor cell when it went into cell cycle. The cells would then produce the virus in the presence of the tumor for a week or two, allowing the gene to transfer, and then treatment with the prodrug could occur. The effect, Dr. Blaese concluded, would be that all of the tumor cells that had acquired the gene

would be killed, and the producer cells that had been introduced would also be killed because they also express the gene. Dr. Blaese then reiterated the effectiveness of this procedure when it was applied in the rats.

Dr. Blaese then presented results of a survival study of some of the initial rats that had been treated. One week following implantation of glioma into the brain, the rats were stereotactically injected at the same coordinates with the producer cells. Dr. Blaese's team then waited an additional week to allow the vector to integrate into the tumor before treating with ganciclovir. Dr. Blaese showed the results of the control animals, stating that all were dead after 2 months.

Dr. Blaese then showed results of experiments using different packaging cell lines for the virus, the first of which used a virus packaged in the PA317 cell line. This cell line represents a mouse 3T3 line, which is one of the retrovirus vector producers that is used clinically to make retrovirus vector supernatant. The results indicated that about half of the animals had long-term cure. Dr. Blaese stated that the experiment had been carried out to almost 1 year in some of the animals, and in approximately 50 to 60 percent of these cases, there was long-term cure from gliomas.

Dr. Blaese presented results of another experiment that used a different packaging line, PAT2.4, which produces a virus that transfers the herpes TK gene. He pointed out that despite a prolongation of survival, this cell line was not as successful as the PA317 cell line. Dr. Blaese then began a discussion of a problem he said is underscored by this experiment.

He stated that, over the years, retrovirus vector producer lines have been established using the amount of virus supernatant obtained as a criterion to measure effectiveness. However, he noted, there has never been a reason to develop vector producer cell lines for *in vivo* use. The results of the experiments using the two different packaging lines illustrate that different lines can have different *in vivo* effectiveness. As a result, much time has been spent trying to determine what makes a packaging line successful for this particular process.

Dr. Blaese then discussed studies of three rats to illustrate how the system works and the spectrum of activity. The first animal was untreated and had only the stereotactic injection of a small tumor into a portion of its brain. It grew a large tumor after 2-1/2 weeks. A second animal was injected with the same tumor, but was also injected with TK producer cells and was treated with ganciclovir. The hemorrhagic tumor was essentially eradicated; one of the striking histologic features of these tumors, noted Dr. Blaese, is that they are hemorrhagic. The third animal had an injection that missed the tumor. Dr. Blaese indicated that this illustrates the problems with delivering the gene, since only three-quarters of the tumor was injected and there was a recurrence of the tumor because the single injection was slightly off the mark.

Dr. Blaese reiterated that the vascular nature of these tumors is an important issue. He showed a slide of a tumor that had been injected with a producer cell line that was making a different vector that carried the gene for beta-galactosidase. Cells that have incorporated this vector, he noted, stain blue when treated with Lac-Z. The vascular endothelial cells immediately adjacent to the tumor were shown on the slide to have incorporated the vector.

Dr. Blaese explained that the ability to kill large tumor masses is due not only to the gene being transferred to the tumor, but also to the fact that the local vasculature is responding to the angiogenic factors being produced by the tumor. The local endothelial cells divide and incorporate the gene and, thus, the vascular supply is killed as well. Dr. Blaese then showed a slide of a tumor section and indicated areas of dramatic hemorrhagic necrosis that occur during the course of ganciclovir therapy.

Dr. Blaese stated that he is frequently asked how the bystander effect potentially works, in addition to what the effect is on the vasculature. He introduced another experiment of *in vitro* gene transfer to illustrate the bystander effect, and noted that the experiment used a tumor suspension of a lymphoma and that various proportions of gene-containing tumor and wild type tumor had been mixed. All of these mixtures were exposed to ganciclovir in tissue culture and the degree of tumor proliferation was observed. He reiterated that with 100 percent wild type tumor in which there is no vector (NV), resistance to exposure to the drug will be exhibited. However, when there is zero wild type, or 100 percent of tumor cells expressing the gene, there will be inhibition of growth. With no bystander effect, he predicted that a 50/50 mixture would yield half the counts, and that is what was observed. Therefore, with this particular tumor there was no evidence of a bystander effect *in vitro*.

Dr. Blaese next described an experiment performed as above except that the 38 colon adenocarcinoma cell line was used. He compared results for the 100 percent wild type tumor and the 100 percent gene-containing tumor. He noted that the results for the 50/50 mixture showed a low degree of tumor proliferation and that even when only 10 percent of tumor cells expressed the gene, there was a great deal of inhibition of proliferation *in vitro*. He said he considers this to be an example of an *in vitro* analog of the bystander effect observed *in vivo*.

Dr. Blaese then reviewed the differences between these two tumors (lymphoma and 38 colon adenocarcinoma). The lymphoma, he explained, is a suspension culture, while the 38 colon adenocarcinoma grows as a monolayer culture and grows on plastic, and the cells come together and there is cell contact. Dr. Blaese stated that, generally, the *in vitro* bystander effect is observed in the adherent cell lines but not in suspension cultures, and that, perhaps, cellular communication via gap junctions is important in allowing the bystander effect to occur.

Dr. Blaese mentioned that his group has isolated a factor from the supernatants of the various cell lines that inhibits the growth of nongene-containing cells, just as a toxic factor can be transferred from the supernatant of the culture to the wild type cells. The current difficulty, however, lies in clearly identifying the toxic factor. HPLC analysis indicates the presence of phosphorylated derivatives of ganciclovir in the media in this situation but, Dr. Blaese stated, it is not clear whether these derivatives are being taken up by the tumor cells from the media itself.

Dr. Blaese then presented an illustration that this general approach can be used to treat other kinds of tumors. A slide was presented showing a liver that had been injected with a tumor. One week later, a stereotactic injection of producer cells was administered at the same site, followed by treatment with ganciclovir. The animal was cured, whereas animals that were not treated with ganciclovir showed massive tumor growth. Dr. Blaese stated that he hopes to

be able to apply this strategy to the treatment of other localized cancers, and that ovarian cancer seems a likely candidate.

Dr. Blaese then discussed his involvement in a Phase I clinical trial of human brain tumors in which five patients with various types of brain tumors have now been treated. The first patient had a renal cell cancer that metastasized to the brain. Because the FDA issued instructions to perform dose escalation, it was necessary to begin the treatment on very tiny tumors. The first patient has had two treatments—his initial therapy and a treatment for a second metastasis. Two patients with glioma and two patients with melanoma have also been treated in the protocol. In general, Dr. Blaese reported, the patients have tolerated the procedure very well. There have been no side effects from the injection, with as many as $5x10^8$ producer cells being injected into the brain. Dr. Blaese also said that some antitumor effect has been seen in patients who have completed their full course of therapy.

Dr. Blaese next discussed problems associated with this procedure. The current difficulty, he noted, is in delivering fibroblast producer cells uniformly throughout the cancer. He said that neurosurgeons have a strategy of visualizing the tumor as a cylinder and then injecting parallel tracks of producer cells throughout the tumor at half-centimeter distances. These parallel tracks are run down the tumor, with cells deposited along them. The virus that is produced then spreads laterally to the adjacent tumor cells. However, Dr. Blaese cautioned, this is not an ideal system because these tumors are infiltrative. He stated that his group is working to develop a more efficient way of delivering the virus from the producer cell out to the tumor cell at a certain location. They are currently attempting to develop producer cells that are motile. One of the best possible cells to use for this purpose, he noted, are glioma cells because they tend to crawl around and are motile. The group is currently producing some packaging cell lines to take advantage of the motility characteristics of these cells in order to achieve effective gene delivery throughout the tumor.

The "ultimate strategy," Dr. Blaese continued, would be to make a replication-competent murine retrovirus capable of infecting cells and spreading horizontally throughout the tumor. This virus would carry a suicide gene and, theoretically, could kill retrovirus using the anti-herpes drug ganciclovir. Under these conditions, the gene could transfer from cell to cell, eventually spreading throughout the entire mass of the tumor. The advantage would be that the nonproliferating normal brain would not take up the gene because it would not integrate into a nonproliferating site. Dr. Blaese said that his group is currently working with this idea and, although he has doubts about its success, he considers it a worthy effort. If, he concluded, a stable, replication-competent virus carrying the suicide gene can be produced, this approach can potentially be used to treat a variety of tumors much more efficiently than is presently possible.

Questions and Answers

Dr. Calabresi thanked Dr. Blaese and congratulated him on his novel approach to this very exciting work. Dr. Calabresi then asked whether Dr. Blaese had considered transfecting TIL cells to help deliver the suicide gene. Dr. Blaese responded that there is a problem with TIL cells in that they are very refractory to transduction with a variety of genes. He has been able to express the TK gene in TIL cells, but human lymphocytes do not replicate the virus

very well. Dr. Blaese said his group has also been trying to use TIL cells as producer cells, but have so far been unsuccessful.

Dr. Wilson asked Dr. Blaese for his current estimate of the life expectancy of the murine producer cells. Dr. Blaese stated that he has data from preclinical studies that were done in monkeys in which beta-galactosidase was used as the vector. He said that cells that had stained blue for the vector were injected into the brains of the monkeys. At 2 weeks after injection, the cells were present in the brains and appeared viable and healthy, but when the animals were sacrificed at 3 weeks after injection, the cells were gone. Dr. Blaese concluded, therefore, that the survival of the producer cells was between 2 and 3 weeks.

Dr. Wilson then asked what immunologic problems might be encountered with the murine producer cells. Dr. Blaese responded with observations on the first patient who was treated with the renal cell cancer and was then retreated. When the initial site of treatment was biopsied approximately 6 weeks after treatment, a large inflammatory response was observed at the initial site of treatment. Dr. Blaese stated that no toxicity was apparent, no midline shift, and no brain edema, but there was an inflammatory response at the site of the initial tumor injection, many necrotic cells, and some clusters of viable tumor that remained at the initial site. Dr. Blaese then said that he did not know what to predict regarding immunologic problems. He said that his group has seen, in some preliminary studies done with brain injections in monkeys, very little evidence of toxicity. However, he said, all of the animals are on very-high-dose dexamethasone that is normally used to prevent brain swelling, and this may have an impact on what is observed.

Dr. Wilson asked Dr. Blaese whether the glioma cells he is considering using as producer cells are of human or murine origin. Dr. Blaese answered that his group is currently looking at both types of cells. He reported that there has been some resistance to using human cells as producer cells because of the possibility that cryptic human retrovirus sequences may somehow be rescued. His group is evaluating this possibility and are also developing producer cell lines in gliomas from rats and mice.

Dr. Becker asked whether Dr. Blaese has considered using this procedure in patients who have had a bladder tumor removed and are at high risk for recurrence. Because the bladder is localized, noted Dr. Becker, it is a privileged site. One could inject the vector directly into the bladder by a simple means and recurrent early tumors might be particularly susceptible to this transfection and destruction. Dr. Blaese responded that although this has not been explored, it is a very interesting and worthwhile idea for further investigation.

Dr. Salmon asked whether there is a potential problem of the replication-competent virus gaining access to other proliferative cells in the body. Dr. Blaese responded that this is one of the issues of concern and that it is an issue of timing. He said this approach has the potential advantage of localizing the virus at the site of the tumor. As it spreads horizontally throughout the tumor, it will stop when it reaches the normal brain tissue, which will not replicate the virus. Dr. Blaese said the virus requires DNA synthesis for integration, and it can potentially gain access to the vasculature and then be spread by the bloodstream.

Dr. Blaese further explained that he has investigated this issue through safety studies in which the retrovirus vector, the TK vector, was injected intravenously into animals, which were then treated with ganciclovir and examined for any systemic toxicity. He reported that, surprisingly, he has not seen any toxicity. However, he continued, this may not be so surprising, because there is a vast array of receptors present for the virus and few of these receptors are associated with proliferating cells. The vast majority of receptors will kill the virus because they will not hit an appropriate susceptible target cell. Therefore, Dr. Blaese concluded, attempts to develop systemic toxicity have not been successful, and this could be one reason why a replication-competent virus might work.

Dr. Salmon asked whether these experiments have been done with replication-competent viruses in animals. Dr. Blaese said they have not, because retroviruses tend to be unstable and rearrange frequently. He said that the theoretical problem is to develop a replication-competent virus that will maintain a TK gene as part of its genome.

Dr. Calabresi asked Dr. Blaese about using a glioma line and whether he would irradiate the line before inserting the gene. Dr. Blaese replied that he would not, but he would select the cell line to be very sensitive to ganciclovir treatment and the suicide gene would be present. He said it would be possible to irradiate, but that the balance between the efficiency of gene transfer and the effects of irradiation must also be evaluated and, he believes, it is possible to succeed without irradiation.

Dr. Calabresi then asked whether Dr. Blaese will continue to work with fluorocytosine system 2. Dr. Blaese said that his group is currently working very hard on this system and that, although it does work, it is not as efficient as TK. They are currently rederiving the clone that is used for the gene because there is evidence of a bystander effect much like that of TK, and, although the level of expression of the constructs is currently low, a major effort with this system is underway. This is one of several other suicide strategies under active investigation, added Dr. Blaese, including some of the mustards that can be linked to other drugs in a prodrug status and then cleaved to make an active drug.

Dr. Wilson asked Dr. Blaese about the motility of the virus injected into the brain. Dr. Blaese said that not much is known, and that the problem is determining how far the virus can travel within a sea of receptors. Although a certain producer cell will easily hit a certain tumor cell, the virus must be able to pass the receptors to accomplish this. He said that, theoretically, it is difficult for the virus to get very far because of the vast number of receptors, and this is one of the reasons a motile producer line or replication-competent virus might allow more uniform spread. Dr. Blaese said the bystander effect is particularly beneficial because it allows for this degree of inefficiency without affecting the profound antitumor effect.

Dr. Broder stated that one of the implications of Dr. Blaese's work is the lack of a complete understanding of what mediates the bystander effect. The tumor regressions observed, he noted, are not entirely due to *in vivo* transfection of thymidine kinase genetic information and that there must be some other phenomenon occurring. Dr. Broder asked whether Dr. Blaese had heard of the term "apoptotic vessicles," suspecting that the meaning of this term is not well defined by those using it. Dr. Blaese responded that he had heard of the term, and Dr. Broder continued by saying that he does not know what it means either.

However, Dr. Broder said, if one had these apoptotic vessicles and could generate them in a regular way, it might be possible to administer a drug at a distant site, under the theory that some tumors are glorified macrophages and these apoptotic vessicles would devour them, making it possible to begin ganciclovir treatment. Dr. Broder asked whether Dr. Blaese believes this is a far-fetched scenario and whether he will pursue it.

Dr. Blaese responded that one of his models showed evidence of the presence of a filterable soluble factor, and that he is currently working to define this factor. Dr. Blaese expressed his concern that the *in vitro* studies may not correlate with what is seen *in vivo*.

Dr. Broder responded that he is pleased with the *in vivo* findings, and that he would rather have an *in vivo* phenomenon that cannot be explained than an *in vitro* phenomenon that does not work out.

Dr. Calabresi thanked Dr. Blaese again for an interesting, stimulating presentation.

X. IMPROVED IMMUNOCONJUGATES FOR IMAGING OF CARCINOMA— DR. JEFFREY SCHLOM

Dr. Rabson introduced Dr. Jeffrey Schlom, noting that he had worked with Dr. Sol Spiegelman on postdoctoral work prior to joining the virology group at the NCI in 1973. Dr. Spiegelman was one of the few people with the knowledge to conduct the reverse transcriptase assay in the 1970s, which Dr. Howard Temin helped to develop. Dr. Schlom began working on mammary tumor viruses at the NCI and eventually developed a panel of monoclonal antibodies from mammary tumors. In 1982, Dr. Vincent DeVita transferred Dr. Schlom into the Division of Cancer Biology, Diagnosis, and Centers. Dr. DeVita felt that moving him into the clinical center from his outlying laboratory would enhance Dr. Schlom's work in developing monoclonal antibodies into clinical reagents useful for diagnosis and the development of new treatments. Dr. Rabson explained that Dr. Schlom's presentation would focus on the outcome of this work.

Introduction

Dr. Schlom said that he would discuss the evolution of a reagent from its inception 13 years ago to FDA approval 2 months ago and share some of the recent innovations in this area. Outlining his presentation, he indicated that he would discuss OncoScint CR/OV, a diagnostic imaging agent for carcinoma; new monoclonal antibodies; use of the intraoperative probe, an area of *in vivo* diagnostics; biological response modifiers and how they enhance tumor detection; and the single-chain antigen-binding protein, which is one result of the studies on recombinant immunoglobulin molecules.

OncoScint Colorectal/Ovarian Cancer (CR/OV)

Dr. Schlom reported that more than 700,000 patients are monitored for recurrence of colorectal (677,000) and ovarian (38,000) cancer each year. He estimated that there are 156,000 new cases of colorectal cancer and 21,000 new cases of ovarian cancer each year.

The OncoScint CR/OV reagent, which is a monoclonal antibody, has been approved for use in conjunction with CAT scanning for the detection of metastatic colorectal and ovarian cancers. Dr. Schlom noted that this reagent is the first antibody-based imaging agent approved by the FDA for use in cancer.

OncoScint CR/OV (antibody B72.3) is an immunoglobulin created by immunizing mice with a human breast cancer metastasis. This antibody is reactive with colorectal, gastric, pancreatic, ovarian, endometrial, prostate, and nonsmall-cell lung cancers; its reactivity to normal tissue is restricted to secretory phase endometrium and transitional colonic mucosa. Phase III clinical trials of the reagent were conducted in colorectal and ovarian cancer; thus, its indications were based on these particular cancers for FDA approval.

Dr. Schlom highlighted the chronology of OncoScint CR/OV. He and his colleagues performed the initial hybridoma fusion in 1979. They published results of the work, filed the patent application with NIH, and began preclinical studies in 1981. Clinical trials began in 1984 at the clinical center with the NIH Surgery Branch and Nuclear Medicine Branch. One year later, results of the initial clinical trials caused Cytogen to license the antibody. NCI published a series of three reviews of the clinical trials in 1987, and the reagent was approved in Europe in 1991 and in the United States by the FDA in 1992.

Dr. Schlom presented a slide of one of the first scans of B72.3 labeled with iodine in a patient with colorectal cancer in the peritoneum 7 days after injection. He began a discussion of the reagent's indications in colorectal studies, derived from Cytogen data that were presented to the FDA. A multicenter Phase III trial using indium-111 B72.3 was conducted with 137 patients, comparing OncoScint CR/OV and CAT scan. Forty-nine percent of lesions were detected by both OncoScint CR/OV and CAT scan, an additional 19 percent by CAT scan only, and an additional 20 percent by OncoScint only. The combined sensitivity was 88 percent.

Dr. Schlom explained that OncoScint is not very successful at detecting liver metastases because liver cells take up and retain the indium-111 marker used in conjunction with B72.3. As an example, he presented a scan of a patient with a tumor detected in the chest and abdomen, which showed a broad outline of the liver. CAT scan detected 84 percent of liver metastases in colon cancer patients, while the antibody detected only 41 percent. Conversely, CAT scans detected only 34 percent of extrahepatic lesions in the abdomen, while the antibody detected 66 percent. Also, 57 percent of lesions in the pelvis were picked up by CAT scans versus 74 percent by the antibody. Concerning the reagent's indications in ovarian cancer, Dr. Schlom explained that occult disease that was confirmed at surgery was detected by the antibody in 28 percent of 103 patients evaluated that had not been detected by conventional means.

Dr. Schlom presented a slide showing a chain of lymph nodes containing ovarian cancer in the abdomen detected by the antibody. He pointed out that CAT scanning and all other evaluations had been negative on patient workup in all the slides presented to this point in the discussion. Comparing CAT scan detection versus OncoScint detection of recurrent disease in the multicenter trial, Dr. Schlom concluded that CAT scan was 29 percent

successful and the antibody was 59 percent successful. Regarding carcinomatosis, CAT scan detected 30 percent and OncoScint 59 percent.

Dr. Schlom presented a slide showing a vial of OncoScint as a final product. He reminded the Board that, prior to FDA approval, OncoScint-CR103 (the antibody's European name) was the first oncologic imaging agent to be approved by countries of the European Community.

Monoclonal Antibodies

About 6 years ago, Dr. Schlom explained, he recognized that there could be other antibodies that react better than B72.3 to the antigen. During the course of 3 to 4 years, he and his colleagues attempted to isolate better antibodies that would react to the same antigen. CC49 ("CC" stands for colon cancer) was the result of this investigation. It reacts to the same tumors as B72.3—all gastrointestinal cancers, and ovarian, endometrial, nonsmall-cell lung, prostate, and breast cancer. Initial clinical trials have shown that CC49 has reacted to more than 90 percent of carcinomas tested and has a higher affinity than B72.3.

To illustrate the *in vivo* work of CC49, Dr. Schlom presented a slide of a mouse xenograft. Because of its higher affinity, this new reagent had a much higher reactivity to a human tumor injected in a nude mouse than B72.3. Dr. Schlom discussed the first four patients with colorectal cancer who were administered I-131-labeled CC49 at Memorial Sloan-Kettering by Dr. Steve Larson in a Phase I trial and showed associated slides. He noted that the imaging characteristics of the CC49 antibody are better than those of B72.3.

Intraoperative Probe

Another potential modality for these reagents is the intraoperative hand-held probe. Dr. Schlom stated that this probe is essentially a Geiger counter, which seeks radioactivity in a tumor. He explained that a radiolabeled antibody, which will seek the tumor, is injected into the patient approximately 2 to 3 weeks before surgery. Dr. Schlom showed examples of the probe searching for occult tumor in the liver prior to surgery, and for residual disease after tumor resection. Dr. Edward Martin at Ohio State University, he continued, is conducting these studies.

Dr. Schlom presented results of a multicenter trial. He recounted that 106 patients were included in a study of 125 I-labeled B72.3 and approximately 100 patients are now being evaluated with the newer antibody, CC49. Based on data from the first 60 patients comparing B72.3 and CC49, Dr. Schlom presented the following figures on detection of various cancers: primary cancer, B72.3 detected 75 percent and CC49, 86 percent; recurrent cancer, B72.3 detected 63 percent and CC49, 97 percent; and occult tumor confirmed by pathology, B72.3 detected 9 percent and CC49, 20 percent.

Dr. Schlom mentioned another good target antigen—carcinoembryonic antigen (CEA)—and showed some tumor slides of CEA. He predicted that, eventually, a combination of antibodies will be injected to detect virtually all tumor masses of a given type.

Biological Response Modifiers

Dr. Schlom discussed the ability to upregulate antigens on the cell surface with biological response modifiers. There are several ways to do this, he explained, and most work in this area has been conducted by Dr. Greiner in the Division of Cancer Biology, Diagnosis, and Centers using recombinant interferons. It is possible, he said, to upregulate antigens on the cell surface with low doses of alpha, beta (ser), and gamma recombinant interferons. Dr. Schlom described the process by which a tumor-associated antigen is expressed on the cell surface. Systemic administration of low doses of recombinant interferons can upregulate the antigen expression and result in more antibody binding to the tumor. This will be manifested by better killing of tumors and/or better localization with a detecting isotope.

Dr. Schlom presented slides depicting results of a Phase I trial conducted in collaboration with Dr. Ernest Borden at the University of Wisconsin. Low doses of recombinant gamma interferon were given intraperitoneally to eight patients. The percentage of positive ascites cells increased in all but one of the cases following the recombinant interferon treatment. Dr. Schlom stressed that these were very low doses of interferon, which caused little or no side effects. Dr. Schlom presented a slide showing the expression of the target antigen before and after interferon treatment. Another slide summarized results of an ongoing trial with colleagues in Rome, Italy, of systemic administration of interferon in patients being biopsied.

Single-Chain Antigen-Binding Protein

Dr. Schlom stated that his last topic of discussion would concern genetic engineering of immunoglobulin molecules. He noted that, whereas hybridoma technology was a quantum leap in serology, the ability to clone and genetically modify immunoglobulin genes is an equally important advance. Dr. Schlom described a collaborative study using a single-chain antigen-binding protein (sFv) as an example.

Dr. Schlom presented a genetic map of a dimeric immunoglobulin molecule. When fragments are made, some of the constant regions are cut off but a certain amount remains, even in the smallest fragments administered to patients. On the other hand, in the single-chain molecule, only a variable region exists, and it is a truly recombinant protein. It can be made in *E. coli*, and not in hybridoma cells, by cloning the variable region of the light and heavy chain and a DNA fragment which corresponds to the 14 amino acid linker.

Dr. Schlom explained that the ability of one molecule like this to detect an antigen depends on the quality of the linker. The linker must give the heavy and light chain appropriate configuration to bind the antigen and must not interfere itself with the antigen binding. Dr. Schlom outlined some advantages of sFvs, including its lower immunogenicity, more rapid blood clearance, more rapid penetration through tumors, and the fact that because it is made in *E. coli*, there are less FDA requirements concerning mammalian DNA and oncogenes. He explained that although there is rapid clearance, the single-chain molecule still has time to bind to the tumor.

Dr. Schlom showed a slide of an *in vivo* study in mice in which there was a substantial difference in clearance of the whole IgG and sFv in the mouse after injection. He added that the single-chain molecule is one of many different recombinant immunoglobulin molecules that he and his colleagues are working with to develop better therapeutic and diagnostic reagents. Dr. Schlom concluded that he and his colleagues are improving these reagents from domain deletions to humanized forms for multiple administrations, and altering variable regions to increase affinity by changing a single amino acid.

Questions and Answers

Dr. Lawrence asked if the new second generation anti-TAG72 antibody is in the pipeline for commercial production and whether it focuses on the liver, which may be a disadvantage. Dr. Schlom explained that TAG72 is not expressed in the liver. Cytogen, he continued, chose to use an indium-111 linker, and all immunoglobulins are metabolized in the liver. It is possible, however, to develop formulations so that this does not happen. He reported that the new anti-TAG72 is in the process of being licensed to two or three companies on a nonexclusive basis for diagnostic imaging.

Dr. Broder commented that Dr. Schlom gave a remarkable presentation. He then asked whether Dr. Schlom envisions using B72.3, CC49, or some derivative in a therapeutic application, linking to an alpha emitter and taking advantage of the interferon phenomenon. Dr. Schlom replied that this use is on the horizon, but the ability of the host to produce an anti-immunoglobulin response has been a drawback. He continued to explain that it has been possible to give injections of these antibodies once, sometimes twice, in Phase I and Phase II trials. Dr. Schlom commented that it is unlikely that a therapeutic agent could be effective with only one administration. Dr. Broder reminded Dr. Schlom that single injections of cyclophosphamide have improved some cases of Burkitt's lymphoma.

Regarding lymphomas, Dr. Schlom noted, success with monoclonal antibodies has occurred in immunosuppressed patients who were given multiple injections of these antibodies. It should be possible to give multiple doses of recombinant humanized antibodies. Dr. Schlom reported that a humanized form of CC49 is in final toxicology testing, and Phase I trials with the chimeric form will begin in 1993. He added that colleagues are working with domain-deleted forms in the laboratory which can clear even faster. Dr. Schlom stated that he is more optimistic of outcome when reagents are administered 5 or 10 times, as opposed to once. A study with autologous bone marrow transplant was conducted at the University of Nebraska, he said, and virtually no second organ toxicity to this reagent was noted. The lack of toxicity implies that more of the reagent can be administered.

Regarding therapeutic applications, Dr. Srivastava asked whether B72.3 or CC49 would internalize the tumor or bind only at the tumor cell surface. Dr. Schlom answered that the antibody binds only at the tumor cell surface. He added that the isotope should be tailored for the antibody in terms of systemic administration, intraperitoneal administration, etc.

XI. AN ECONOMIC ASPECT OF CANCER CARE—DR. MARTIN BROWN

Dr. Greenwald explained that, during the past decade, there has been a trend in the NCI surveillance program to expand its scope. In the past, the program was essentially a cancer registry effort (SEER) to monitor incidence, survival, and mortality rates. The Institute now realizes that it needs a systematic body of information about health care, health financing, and patterns of care, which helps define the relationship between economics and science.

Dr. Greenwald introduced the next speaker, Dr. Martin Brown, an economist with the Applied Research Branch of the Division of Cancer Prevention and Control (DCPC) Surveillance Program.

Introduction

Dr. Brown began his presentation by acknowledging the collaboration of many colleagues in the Division of Cancer Prevention and Control (DCPC). He expressed his hope that the collaboration among epidemiologists, biologists, statisticians, and clinicians will help bring cancer-related health economics into the purview of science. Dr. Brown presented several slides showing the collaborative effort's priority areas of research: lifetime treatment costs of cancer; cost evaluation and effectiveness evaluation of cancer prevention and control research; health care interventions; and characterization of the economic burden of cancer on the family and society.

Dr. Brown presented a slide with figures provided by the Health Care Financing Administration to help explain the current national concern about health care expenditures in the United States. According to HCFA projections, if the same factors that determine health care costs today continue to function until the year 2000, health care expenditures will increase from $675 billion in 1990 to $1.7 trillion in 2000—an increase from approximately 12 percent of the gross domestic product to about 18 percent. These data, Dr. Brown added, have caused much concern about the accommodation of health care costs in the future. He pointed out that although it is not necessarily inappropriate to spend nearly 20 percent of the gross domestic product on health care, there is a great deal of concern about whether the U.S. population is receiving the optimal amount and the highest quality of health care, given the dollars that are spent.

Currently, Dr. Brown stated, it is not possible to determine disease-specific expenditures in the United States, because an economic census of disease does not exist. There are two separate, and incomparable, accounting systems that look at health care finance in the United States. Dr. Brown explained that the DCPC has used indirect methods to derive global estimates of $35 to 40 billion for all cancer-related health care expenditures in 1990. Not surprisingly, the most common cancers—breast, colorectal, lung, and prostate—accounted for the highest expenditures. The DCPC looked at the composition of expenditure attributable to initial care, terminal care, and continuing care, and patterns were found to differ by cancer sites. Dr. Brown cited as an example the fact that while continuing care accounts for a high percentage of total expenditures for breast cancer, which has a relatively long median survival rate of 9.5 years, this percentage is much smaller for lung cancer, which has a short median survival rate. He noted that these decompositions by phase have various economic

implications in the evaluation of various types of intervention, prevention, screening, adjuvant treatment, and treatment and rehabilitation.

Dr. Brown stated that in discussions about health care reform, three goals are often expressed: 1) global expenditure control; 2) universal access; and 3) high-quality care. A variety of mechanisms have been proposed to achieve these goals, such as reimbursement limits, practice guidelines, managed care and utilization review, and fully informed patient/physician decision making. Dr. Brown commented that none of these mechanisms can function optimally without a great deal of information about efficacy, effectiveness cost, efficiency, resource distribution, and access. Dr. Brown and his colleagues within the DCPC feel that it is important to systematically collect and scientifically analyze information of this type.

Dr. Brown quoted a statement by health economist Louise Russell in a 1989 *Science* article: "If decisions about medical care are to be made well, alternative ways of using resources must be compared." Dr. Brown explained that cost-effectiveness analysis is used to evaluate the opportunity costs of decisions in medical care. It comprises principles and methods for estimating the resource cost and the health effects of alternative medical interventions. He stressed that all cost-effectiveness analyses are comparative.

Dr. Brown reviewed three research projects in the Applied Research Branch concerning cost and cancer: 1) database linkage of cost and cancer; 2) analysis of the cost-effectiveness of adjuvant therapy for colon cancer; and 3) analysis of efficient distribution of breast cancer screening resources.

Database Linkage of Cost and Cancer

To overcome the aforementioned problem of the disjointed accounting systems, the Applied Research Branch has linked the SEER cancer registry system to Medicare claims records from 1984 to 1990. The Medicare database contains all billing information under Medicare, which will allow Dr. Brown and his colleagues to produce data on the lifetime expenditure and resource utilization for cancer, total Medicare payments on a per-patient basis, and costs that are specifically attributable to cancer for those patients. It will allow the Applied Research Branch staff to produce improved and more current aggregate estimates of cancer-related costs and provide detailed cost information for input into cost-effectiveness studies. It will also be possible to conduct studies of treatment patterns using the treatment information in SEER and the detailed coding information in the Medicare database.

Dr. Brown presented a slide of the preliminary results of total lifetime expenditures for three main cancer sites—breast, prostate, and colorectal—by the stage at diagnosis. Final results will be submitted for publication. Dr. Brown pointed out that these are expenditures from the time of diagnosis to the time of death for Medicare patients. He noted that expenditures for self-administered prescription drugs and unskilled long-term care are not included in the estimates, because these expenses are not covered under Medicare. Dr. Brown elaborated that these are expenditures for cancer patients, not expenditures specifically attributable to cancer. The Applied Research Branch is developing methods to generate estimates of costs attributable to cancer for a forthcoming paper. Contrary to common

perceptions, Dr. Brown stated, total lifetime cost for patients diagnosed with distant disease is less than for patients diagnosed with local or regional disease, which has implications for evaluating certain interventions. This information has been unavailable previously because of the lack of cost and expenditure information based on the stage at diagnosis.

Analysis of the Cost-Effectiveness of Adjuvant Therapy for Colon Cancer

Dr. Brown discussed the Applied Research Branch's investigation of the development of adjuvant therapy for colon cancer, combined chemotherapy for stage III colon cancer, from an economic viewpoint. Dr. Brown and his colleagues used cost data, crucial results of NCI-sponsored trials, and a variety of other data sources to evaluate the return on NIH investment and the potential cost-effectiveness of this intervention. Using a computer-simulated scenario, they examined treatment for all eligible patients from 1990 to the year 2000 and evaluated all subsequent costs and benefits over the period from 1990 to 2020.

Dr. Brown presented a slide showing the cumulative net cost of treating the population with this intervention—net cost because by preventing recurrence, the treatment saves costs associated with recurrence and, thus, counteracts the initial cost of the treatment—and the cumulative benefits in terms of thousands of life years saved. He noted that the costs of providing treatment tend to accumulate early in the time period and the benefits catch up later, which is true of most cancer-related interventions. Dr. Brown added that this fact is even more valid for screening and prevention than for adjuvant therapy. He explained that he and his colleagues ran a computer simulation rather than examining observational data because observational databases cover only a short period of time and miss most of the benefits that result from these types of interventions.

Dr. Brown presented another slide summarizing the results of the study. Cost-effectiveness estimates reveal 385,204 life years saved and $774 million total net cost of the intervention, resulting in a cost per life year saved of $2,094. Dr. Brown pointed out that this is a very cost-effective intervention by normal standards, since most interventions in the health care system range in the tens of thousands of dollars per life year saved. He stated that his colleagues adjusted for quality of life, because of toxicity and inconvenience associated with cancer treatment. There was no effect on outcome, even with the adjustment, because toxicity is relatively mild over a short period of time. The benefits of avoided recurrence and its associated low quality of life eclipse the initial toxicity downside.

The slide also showed an estimate of the social return on the NIH investment. Life years saved were valued using an economic value of potential earnings, which, Dr. Brown explained, is the standard method for cost-of-illness studies. Dr. Brown and his colleagues estimated the NIH research investment at $11 million and the net cost of intervention at $338 million, resulting in a net return to society of approximately $1.7 billion. The rate of return on this investment was estimated at 33 percent.

Controversy and conceptual problems surround the valuing of life years saved. In terms of this investment project, Dr. Brown suggested that it be considered that for a cost of $11 million, society and the clinical community will receive definitive evidence that this intervention is efficacious and cost-effective. Dr. Brown informed the Board that the Applied

Research Branch is conducting patterns-of-care studies using the SEER database to track the actual adoption rate of this treatment over the next few years. It remains to be seen whether the adoption of this treatment will coincide with the computer-generated scenario.

Analysis of Efficient Distribution of Breast Cancer Screening Resources

Dr. Brown explained that a 1987 study by the Office of Technology Assessment showed that breast cancer screening is cost-effective at about $55. This report influenced Congress to pass a provision in which breast cancer screening is covered under Medicare. Also, many States have mandated third-party coverage for breast cancer screening. Dr. Brown reported that 70 percent of all employer-provided health care plans cover mammography.

Dr. Brown presented a diagram of a cost analysis of delivering mammography screening services. He pointed out that there is a relationship between cost and the number of mammograms delivered per day in a facility. Cost increases if the volume of mammograms is below 10 or 15 examinations per day, and decreases if the volume is in excess of 15. The current Medicare fee is about $57. To deliver mammography at this cost, a facility would have to conduct more than 15 screenings per day. A national representative survey revealed the actual utilization in 1992 to be less than 10 mammograms per day, at a cost of about $80. On average, patients were charged about $104 for a mammogram in 1992.

Dr. Brown explained that less than half of the 10,000 mammography facilities in the United States are accredited by the American College of Radiology. There is concern that the Mammography Quality Assurance Act, which requires every facility to receive accreditation and annual inspection, may reduce access to screening in this country.

Dr. Brown presented a slide depicting the number of mammography facilities per health care service area, as defined by the National Center for Health Statistics. The diagram shows that about 80 health care areas should have a minimum of two machines, but about 80 health care areas are shown to have between 27 and 420 machines. According to Dr. Brown's diagram of efficient usage, more than 300 health care areas would have no mammography facilities within their bounds. Currently, there are only 50 health care service areas without a facility. The 300 areas contain only 6 percent of the eligible population. Dr. Brown explained that it might not be the best way, but it would be possible to provide at least one machine to those 300 service areas by redistributing from areas where there is an overcapacity of machines.

Conclusion

In conclusion of his presentation, Dr. Brown presented information on areas in which the Applied Research Branch has made substantial progress and areas in which more research is needed. Data are available, he said, from Medicare and SEER Medicare in terms of lifetime treatment costs, as well as from several studies with records of health maintenance organizations (HMOs). Almost no information is available, however, from fee-for-service settings; since this is the setting in which most people receive their health care, more studies are needed in this area. Dr. Brown mentioned that there are a number of ongoing and potential studies on cost-effectiveness evaluation of cancer prevention, control, research, and

interventions. More studies in the area of prostate, lung, colorectal, and ovarian cancer screening, he said, are needed.

Dr. Brown pointed out that, surprisingly, there are little data on the economic burden of cancer on the family and society. There are some aggregate estimates that were presented at a workshop in April of 1992 and there are estimates from convenience samples, but there are few estimates based on representative samples that are generalizable in a rigorous sense.

Dr. Brown stated that in order to perform good cost-effectiveness and cost-benefit analyses, a database of economic and quality-of-life data are needed. He noted that there are efforts to collect this type of data in the context of cancer prevention and control clinical trials.

In conclusion, Dr. Brown stated that he and his colleagues in the Applied Research Branch believe it is important to identify interventions in which the cost information and the cost-effectiveness framework make a difference in whether intervention is viewed as desirable.

Questions and Answers

Dr. Sigal asked if Dr. Brown's estimate of $40 billion per year for cancer treatment is comprised entirely of third-party costs and where Dr. Brown obtained these statistics. Dr. Brown answered that various sources were used for estimation. Various studies conducted by the National Center for Health Statistics in the 1980s were consulted to derive some components of the cost; the National Hospital Discharge Survey was examined for in-hospital cost; the National Ambulatory Care Survey was looked at for outpatient cost; and various other studies were analyzed and compiled to derive an aggregate estimate. Dr. Brown explained that, in a *Journal of the National Cancer Institute* article published 2 years ago, he took the increased number of cancer cases and medical care component of the cost of living into consideration and updated the estimates for 1990. He noted that estimates presented at this NCAB meeting are from a different source and are based on Medicare charges, not reimbursements, but are very similar to those in the journal article. Using SEER data from 1973 to 1989 on cancer incidence and survival, Dr. Brown continued, he constructed these estimates of the aggregate annual cost in 1990. These, he said, are the best data currently available.

Dr. Sigal then asked if insurance carriers have reliable data. Dr. Brown replied that health care accounting in the United States generally is based on billing episodes, not on a disease-specific basis or longitudinal individual-person basis. It is difficult, therefore, to construct lifetime cost or aggregate cost estimates from most insurance claims bases. Dr. Brown added that talks are ongoing with managed care consultants, and third-party payers are attempting to organize their data into a form that is more useful for research purposes.

Dr. Srivastava asked what is the average life expense per patient in Medicare payments from diagnosis to death. Dr. Brown answered that the expense varies by cancer and stage, and this information will be coming out in a paper in the next 6 months. He added that the average survival time for different cancer sites influences total lifetime expenditures.

Ms. Mayer expressed concern about assigning a dollar amount to years of life. She said that the data presented on local versus distant disease suggest that it is cheaper not to treat patients or to wait until they have metastatic disease. Ms. Mayer asked whether there is another way of presenting this data to convey the difference between the amount of cost and years of life.

Dr. Brown answered that the point of this presentation was to provide data that allow this type of analysis to be conducted. He explained that the Applied Research Branch sees its responsibility as a national resource in the area of economics and cancer to develop systematic and reliable databases that can be used to conduct cost-effectiveness analyses. They also try to formulate methodologies to help others utilize the data appropriately. One project underway is a revision of CANTROL (a computerized program for aiding cost-effectiveness analyses), which will incorporate these databases and incorporate methods and tutorials for evaluating interventions. Dr. Brown noted that this has been problematic in the past because some people have not evaluated lifetime costs carefully and have made indefensible claims, such as that breast cancer screening saves money. Almost no new health care intervention, Dr. Brown stated, costs society less money. The issue, he continued, is what is the health benefit received for dollars spent. Dr. Brown said that the point of cost-effectiveness analysis is to tell us how to get the most health benefit for the dollars spent, not whether we will save money, although there are some interventions that may result in aggregate cost savings.

Dr. Salmon asked whether Dr. Brown has an estimate of the reliability of the projections presented. Dr. Salmon added that many of the calculations are based on clinical assumptions that are difficult to validate and many of the cost estimates are based on parts of the population. For example, Dr. Salmon presumed that calculations about adjuvant therapy of colon cancer are based on results of the clinical trials. Dr. Brown affirmed Dr. Salmon's statement and explained that he and his colleagues conducted a sensitivity analysis to examine key assumptions, assigned them large confidence intervals, and studied to what extent the confidence intervals affected the calculation. He noted that it is often difficult to determine whether the generated confidence intervals are reflective of the actual confidence intervals.

A new approach, continued Dr. Brown, is to conduct Monte Carlo simulations of both the clinical data and the cost data to generate statistically valid confidence intervals. The Monte Carlo simulations, however, are rooted in a database of the clinical results, and these databases are not well developed. Regarding the SEER Medicare estimates, Dr. Brown said that he and his colleagues are generating statistically valid confidence intervals that take measurement error into account. They do not address the issue of external validity, reliability of patients in different settings, and differences in those costs. Dr. Brown explained that this is why the Applied Research Branch is conducting HMO studies to access a different age group and would like to conduct more studies in the fee-for-service setting. Dr. Brown concluded by noting that there is an acknowledged weakness in this area.

XII. THIRD-PARTY REIMBURSEMENT OF CLINICAL TRIALS— DR. O. ROSS MCINTYRE

After a brief recess, Dr. Calabresi introduced Dr. Michael Friedman, Associate Director of the Cancer Therapy Evaluation Program, who would introduce Dr. Ross McIntyre, Professor of Medicine at the Norris Cotton Cancer Center in Lebanon, New Hampshire.

Dr. Friedman stated that many groups—patients, investigators, the research community, those who sponsor research, and the insurance industry—are interested in the question of how to reimburse for clinical investigation. He explained that Dr. McIntyre would speak to the Board on this topic as a representative of the research community. Dr. Friedman pointed out that not only is Dr. McIntyre a professor at Dartmouth Medical School and the former director of their cancer center, he serves as the chairman of CALGB, one of NCI's national cooperative groups. Dr. Friedman added that Dr. McIntyre has direct experience with some of the difficulties and innovative solutions for dealing with this problem, which he would share with the Board.

Introduction

Dr. McIntyre began his presentation by discussing problems associated with the issue of third-party reimbursement. Dr. McIntyre commented on the inappropriateness of receiving a claim denial by telephone from a person who does not understand the medical terms included in the claim. He told an anecdote about an insurance company's denial of payment for a Hodgkin's disease treatment because the drugs used in the MOPP regimen were "off label." That is, drugs used in this curative combination for therapy were viewed in this case as experimental because their package inserts do not include descriptions of the combination therapy regimen.

From a review of this issue and its impact on clinical trials by Dr. Michael Friedman and Ms. Mary McCabe in the *Journal of the National Cancer Institute*, Dr. McIntyre read a proposal in the article's conclusion: "All reimbursers of health care (private and public) should reimburse the clinical care costs (within the financial agreements of policy provisions) but not the research costs associated with patient participation in NCI-sponsored therapeutic clinical trials." Dr. McIntyre commented that the debate on this topic among health care providers, patients, and insurers has led to several States passing laws requiring insurers to pay for the off-label use of drugs.

Outlining his presentation, Dr. McIntyre announced that he would discuss his firsthand experience with the CALGB's negotiation of support for a protocol with the Blue Cross Association, define clinical care and research, discuss strategies of coercion used by the clinical research and patient advocate communities, discuss possible resolution of this issue, and offer his views about the risk to creativity embodied in policy development.

Negotiation of the CALGB-9082 Protocol

Dr. McIntyre discussed the CALGB-9082 protocol, which is a randomized comparative study of high-dose chemotherapy with autologous bone marrow transplantation versus standard-dose chemotherapy as adjuvant and consolidation therapy to patients with operable

stage II or stage III breast cancer involving 10 or more axillary lymph nodes. It is a CALGB–led intergroup study and includes the Southwest Oncology Group and the National Cancer Institute of Canada. The study is chaired by Dr. William Peters at Duke University. The concept for this protocol was approved on July 18, 1989; the first draft of the protocol was written in September of 1989 and sent to NCI for consensus review in November of 1989. One year later, the CALGB sent revisions to the NCI on November 26, 1990. The protocol was approved by NCI on January 14, 1991, and activated by CALGB on January 20, 1991.

Dr. McIntyre explained that the long negotiation of CALGB-9082 concerned whether costs of the protocol would be reimbursed or a contract that represented a less-than-cost reimbursement would be issued. Negotiations were complicated by the longstanding adversarial relationship that existed between the insurance industry and the clinical researchers. An agreement was reached in which the insurers would pay less than the actual cost of the procedure. The hospitals that signed the contract subsidized the clinical research project with private, charitable gifts and by raising charges to those who could afford to pay or who had other insurance.

The Blue Cross Association, Dr. McIntyre explained, felt that it gave the involved institutions a bargain and that the institutions should be required to pay part of the cost of the research because of the prestige they would gain through participation in this national trial. The clinical investigators experienced resentment from hospital administrators for causing financial strain that resulted in off-loading costs onto other patients and their insurers. Since costs differ across the country, Blue Cross decided to pay different institutions various amounts of reimbursement, depending on locality and State funding. Dr. McIntyre mentioned some other controversial issues. Those leading the study insisted that each transplant institution enter three preliminary patients to gain experience with peripheral blood stem cell support and to demonstrate competence with the transplant ablative regimen. These patients were not required to meet eligibility requirements of the randomized part of the study, but they had to be participants of an approved protocol. Dr. McIntyre explained that it took a long time to resolve how to obtain G-CSF for the preliminary patients because it could not be obtained via the usual mechanisms for provision of an investigational drug.

Finally, Dr. McIntyre explained, it was necessary to educate the Blue Cross Association about a cooperative group and vice versa. The Blue Cross Association is not a Blue Cross plan, which is the actual insurer. The plans make payments to the Association. The Association wrote the contract that went to the institutions, and the plans could then state that they were not supporting research. The Association was, in fact, supporting the research, and it felt that this was an important position to maintain. Subsequently, there were questions regarding the role of the insurer, which could be viewed as a sponsor of the research, and the appropriate level of scientific input by insurers and their national organizations. One recent issue has been the Blue Cross Association's request for representation on the study monitoring committee, which has access to the actual data concerning efficacy of the randomized part of the study and makes decisions on the continuation of the trial.

As of February 1993, Dr. McIntyre reported that 165 patients were registered to the randomized part of the study. The study is ahead of schedule and should be finished a year earlier than projected. Of these 165 patients, the Blue Cross Association registered 15.

Fourteen of those 15 patients have been treated with support from Blue Cross Association dollars, and 11 of 165 patients have been randomized by institutions that received contract support for the participation of those particular patients in the study. Other patients have either had their costs paid by insurers or had substantial out-of-pocket expenses.

In conclusion, the Blue Cross Association indicated a willingness to support the evaluation of new technologies. It issued press releases that may have informed the public about the efficacy of the procedure. Its endorsement suggests that the technique is worthy of legitimate inquiry but probably has had little effect upon accrual to the study.

Definitions of Clinical Care and Research

Returning to the quoted statement by Dr. Friedman and Ms. McCabe, Dr. McIntyre reiterated that the insurer should cover the clinical care costs of an NCI-sponsored trial. He suggested that it is important to consider what constitutes an NCI-sponsored trial, and stated that trials conducted by a cooperative group, funded and approved cancer centers, and with P01, R01, or SPORE grant support are presumably NCI-sponsored trials. It is less clear, however, whether trials listed in PDQ are sponsored by NCI.

Dr. McIntyre asked who should be responsible for the costs of extra testing, staging, prognosis determination studies, or special testing to detect minimal residual disease or to diagnose an early recurrence that allow for better outcome analyses, but are unrelated to treatment received by the patient. Also, who should pay for the determination of *in vitro* chemosensitivity? These are important questions, Dr. McIntyre stated, because most grants do not contain significant amounts for the reimbursement of research-related clinical expenses.

Dr. McIntyre suggested that trying to define research and clinical care sets up a dichotomy, which is harmful both to the patient and to the legitimate process in medicine. He then read statements that appear on consent forms, which indicate the state of this problem: "In the event that complications occur as a result of this treatment you will be provided with the necessary care. However, you will not automatically be reimbursed for medical care or receive other compensation as a result of any complications . . . . Investigational drugs used in this study are supplied to you without charge, sometimes by the Division of Cancer Treatment or sometimes by a pharmaceutical house. If these agents become commercially available during the course of the study, however, you may be asked to purchase subsequent doses of the medicine." Regarding the latter statement, Dr. McIntyre cited the example that taxol in breast cancer is in clinical trial and asked when breast cancer patients will be required to start buying taxol now that it has been approved for treatment of ovarian cancer. In essence, he said, CTEP, the cooperative group, and others are endorsing the off-label use of drugs for experimental purposes.

Clinical Research and Patient Advocate Strategies

Due to the frustration of physicians and patient advocacy groups, Dr. McIntyre stated, policy development at the State level could have long-term negative implications for evaluation of new techniques. For example, he continued, as a result of patient and physician activism, health insurers and HMOs in New Hampshire are now required by law to cover bone

marrow transplantation on NCI-approved clinical trials. Dr. McIntyre explained that this legislation passed the New Hampshire House and Senate because female representatives demanded a roll call vote, and any person who voted against this bill that generates support for marrow transplantation in breast cancer was categorized as a male chauvinist.

Five States now mandate insurance coverage for off-label use of commercially available drugs. Insurers in New Hampshire expressed their belief that they should not be required to operate under mandates. Those opposed to the insurers' viewpoint noted that there are more statutes in New Hampshire concerning insurance companies than there are for criminal justice. Dr. McIntyre explained that he used these anecdotes to help explain why he believes it is necessary to enact a national policy on clinical research in the United States. He added that this is a critical issue that should be dealt with at this time, since the national health care system is being evaluated.

Dr. McIntyre stated that the number of reports concerning clinical trials coming from Europe and Japan is astounding. He told the Board about a trip on which Dr. Calabresi led the New England Cancer Society to Italy. Investigators from Bologna described approximately 30 allogeneic bone marrow transplants for patients with multiple myeloma in a system in which their national health plan facilitated a careful assessment of this technology. Dr. McIntyre stressed that the United States will lose its international leadership position in conducting high-quality clinical trials unless action is taken.

Dr. McIntyre stated that there is an interest in effective testing of new technology before widespread introduction, but there is no system to allow this to happen. The change agent and the payer for patient care, he continued, are uncoupled, and it is therefore difficult to answer questions that may be of great economic importance.

With the help of slides, Dr. McIntyre described an incident at his medical center in which a surgeon used an experimental procedure discussed in the February 1986 issue of *Archives of Surgery*. An article in this journal described 31 patients in whom a zipper had been placed in the anterior abdominal wall to facilitate repeated access to the abdominal cavity. A 61-year-old woman was admitted to a hospital with sepsis and shock. After resuscitation, staff noted a hyperosmolar state with a glucose of 800 milligrams per dl. A CAT scan showed gas in the retroperitoneum from the diaphragm to the pelvis, and a pleural effusion cultured *E. coli*. Pneumothorax resulted from a Swan-Ganz catheter placement at the local hospital, and the patient was transferred to the Dartmouth Hitchcock Medical Center 24 hours later.

On admission, staff instituted triple antibiotic coverage and other support measures and performed emergency surgery. Postoperatively, the patient was in critical condition with ventilatory support. The surgeon involved in this patient's care recognized that multiple debridements would be required to control the sepsis. On the second day of hospitalization, the surgeon carried out the experimental procedure with the zipper to facilitate the required repeated laparotomies. The pancreatic bed was examined and debrided on seven occasions during the next 30 days. Repeated bouts of sepsis and other major complications occurred. After slow improvement, the patient was discharged 80 days after admission.

Dr. McIntyre reported that the total cost of medical care for this patient was $121,000. If the zipper had not been inserted, the patient would have died by the end of the first week and the cost of the patient's bills would have been $15,000. Thus, the cost of the medical advance was nearly $106,000. Dr. McIntyre rhetorically asked if the cost of the experiment was the cost of the zipper or the cost of the medical advance. He explained that if this 68-cent zipper had been sold by a hypothetical Acme Medical Products Company, the cost of the zipper would likely be $1,700, due to the costs of development, documentation of its source and composition, sterilization, packaging, preclinical testing, clinical testing, product liability insurance, quality assurance, shipping and handling, salary of the detail person, advertising, returns of the outdated product, and profit margin.

Dr. McIntyre noted that statements in the *New England Journal of Medicine* from zipper industries warning against the use of zippers in humans were issued soon after the procedure was written up.

Dr. McIntyre suggested that insistence of FDA approval and pharmacopeia of the zipper would: 1) diminish the risk to the patient; 2) reduce the risk of a malpractice claim; 3) allow reimbursement; 4) increase the cost of medical care; 5) provide employment to many; 6) arrest the evolution of zipper design; 7) result in an amusing package insert; and 8) shackle another dimension of man's adventurous spirit.

Dr. McIntyre next presented a model for clinical investigation that he devised several years ago. He believes that the current system should be revised so that: institutions are licensed to conduct human research; approved institutions are audited to maintain the license; testing of new drugs and devices is allowed only at approved institutions; the core cost of clinical research at licensed institutions is funded by peer-reviewed CRC-like mechanisms; and society assigns responsibility for payment of all costs for patients on research treatments to the current payers of treatment costs—insurers, Medicare, Medicaid, etc.

Dr. McIntyre suggested that it is necessary to decide what fraction of the total dollar amount generated by the health care industry should be allocated to research and development. It would then be necessary to decide where this money could best be spent and who could best award it. Dr. McIntyre added that he thinks that, currently, the insurance industry is bearing much of the cost of clinical research. He recommended that the Nation develop a comprehensive, effective means of evaluating new technologies in the setting described above prior to their being reimbursed by any payer.

Questions and Answers

Dr. Day asked the NCI for estimates of the magnitude of clinical research occurring under peer-reviewed auspices and associated costs. He added that there will be a great deal of interest in this topic on the State and national levels and requested that this information be presented at a future NCAB meeting. Dr. Day noted that the Subcommittee on Cancer Centers discussed at their meeting the importance of routinely collecting data from the centers.

Dr. Calabresi answered that this request will be noted.

Dr. Bettinghaus asked Dr. McIntyre how many of the 165 patients were indigent and had no insurance at all. Dr. McIntyre explained that this information is being collected and that he will not have access to it until the study is ready for analysis.

Dr. Salmon commented that many research protocols require extensive, although routine, testing, such as CAT scans and MRIs, which is declined by HMOs and PPOs. He stated that there needs to be an accommodation in which either less extensive testing is conducted or the testing is underwritten. He continued by noting that at least 5 percent of the total budget in the economic sector is focused on research and development, sometimes more. Dr. Salmon said that an argument could be made to the health care industry that health care research comprises less than 5 percent. Dr. McIntyre replied that the development of a protocol is similar to the design of the armored personnel carrier carried out by the Department of Defense—some specifications are developed and then 100 people comment on it; one is not considered an academic unless he or she can suggest an improvement to the existing plan. Dr. Salmon added that this is called the Christmas tree protocol—everybody keeps adding another ornament until the tree collapses.

XIII. SUBCOMMITTEE REPORTS — DR. PAUL CALABRESI

Subcommittee on Aging and Cancer

Ms. Mayer reported that two presentations were made during the subcommittee meeting. First, Dr. Ungerlieder from the DCT provided an overview of the Institute's clinical trial activities regarding patient accrual. Data presented on protocols dealing with the most prevalent sites of cancer in the elderly generally indicated that subjects aged 65 and over are underrepresented relative to the prevalence in that age group. A variety of reasons for this situation were discussed, as well as study initiatives underway at DCPC to identify the existing patterns and explore alternatives to increase patient accrual.

Dr. Rosemary Yancik from the National Institute on Aging (NIA) presented data on ongoing studies on patterns of patient care. She also discussed joint initiatives between NCI and NIA, particularly those concerning ovarian cancer and the utilization of foreign populations for which data on the elderly has reached a more advanced level than in the United States.

Due to time constraints, Ms. Mayer announced that further discussion of the gaps and barriers related to cancer research and the elderly will continue at the subcommittee's next meeting.

All members were in favor of the motion to approve the subcommittee report.

Subcommittee on Cancer Centers

Dr. Salmon reported that his subcommittee discussed the importance of the new clinical research and P01 task forces which are integral to the activities of cancer centers. The

subcommittee also reviewed center guidelines relating to prevention and control and debated whether or not a cancer center without an approved prevention/control program can be considered comprehensive.

The cancer center database was also discussed, and it was recommended that the program staff produce an annual report through the subcommittee. This report, intended for publication, will incorporate data submitted on the standard cancer centers data forms and will be made available to the subcommittee and all the centers. The centers will then use the data to identify composites and make comparisons among themselves relevant to future planning based on previous accomplishments. The first report by the centers program staff will be submitted at the February 1994 meeting, following the presentation of an outline at the next subcommittee meeting and a discussion of the report in the fall.

The subcommittee then addressed proposed revisions in the OMB Circular A21, published in the *Federal Register* on December 9, 1992, as they relate to the centers program and other programs for which the issue of charging administrative support as a direct cost is relevant. Subcommittee members did not have the opportunity to review the OMB publication before their meeting. Therefore, noted Dr. Salmon, its meaning is not yet clear, and Dr. Rabson has offered to check with the NIH attorney to ascertain whether or not the Circular A21 revisions actually indicate that an administrative component may no longer be included in various grants, including P30s, P50s, U01s, and U10s. The revised Circular A21 states that administrative costs such as those for secretaries or data collectors, as opposed to those for research technicians, will be covered by indirect costs, with a cap of 26 percent, rather than being part of the direct cost of the grant. This, Dr. Salmon stated, is where the central issue lies with grants in which administrative costs are particularly important. The subcommittee felt that this issue was sufficiently important to draft a resolution to be filed with the OMB as a protest, should the proposed changes in Circular A21 indicate that an administrative core component will no longer be supported in the aforementioned grants. Dr. Salmon then read the proposed resolution:

> As the principal advisory body to the National Cancer Institute, the National Cancer Advisory Board urges the Office of Management and Budget not to implement its proposed revisions to Circular A21 as published in *Federal Register* pages shown in relation to a specific set of its research support mechanisms wherein the research to be conducted is specifically dependent on the central administrative components of the award and would be damaged by the proposed revisions. We believe that these awards must be exempted from the proposed revision in A21, as represented by the National Cancer Institute's highly successful Cancer Centers Program, which include its P30 cancer center support grants, P50 specialized centers of research excellence, P20 planning grants, and its program project, P01, grants and cooperative agreements including U01 and U10 awards, multi-institutional cooperative groups, contracts, and other award mechanisms.
>
> For these types of awards, the research objectives to be achieved are integrally dependent on the viability of the administrative core component or a coordinating center which is an essential direct cost. The National Cancer

Advisory Board, therefore, vigorously opposes the proposed shift of the administrative component of these specific award mechanisms to the indirect cost category, as this change would seriously compromise the ability for these research initiatives to be successful.

Dr. Wilson requested that Dr. Salmon explain why placing the same amount of money under indirect costs results in a loss to the investigator for the project. Dr. Salmon responded that policies relating to the use of indirect costs among public and private universities differ widely across the country. Some institutions may use indirect costs to fully support a project, while others may allocate a substantial portion to the State legislature. For example, the headquarters grant to a cooperative group may be $5 or $7 million to one location in one institution, possibly even off-campus to reduce the indirect costs, while the participating research institutions are in other locations as separate units. There is no indirect cost category in this case from which such a substantial amount of funds could be recovered. Similarly, this would apply to the administrative core and senior leadership components of a center grant, program project or SPORE, or certain cooperative agreement. U10s, many of which are multi-institutional, may have one institution that serves as an administrative core without any research projects. Dr. Salmon said he believes that the Circular A21 revisions are intended to influence the decisions made by an institution regarding which funds stay within the institution and which are apportioned elsewhere.

Mrs. Bynum noted that Ms. Tisevich had just furnished an update of the A21 proposed revision. Since a freeze had been implemented on all proposed rulings, the Board would be able to convey its thoughts on the matter to OMB with the understanding that no action would be taken at the present time. All were in favor of the motion to approve Dr. Salmon's report.

Clinical Investigations Task Force

Dr. Calabresi reported on the first meeting of this task force, noting that their primary goal was to arrive at a diagnosis of the problem. It was determined that this problem or illness lies not within the number of researchers going into clinical investigation nor a lack of support for them, but, rather, in the translational area involved in the transfer of research from the laboratory to the bedside.

Presentations were given by Drs. Michael Friedman, Brian Kimes, and Roy Wu, and Ms. Diane Bronzert related to a history of past problems. The task force reviewed their systems and a substantial amount of data that had been collected and analyzed, finding much information that will prove helpful in the future.

In a future meeting, the task force plans to arrive at a more specific diagnosis and recommend some form of therapy. Dr. Calabresi thanked the staff, particularly those individuals who collected the data the task force will be analyzing to come to grips with this problem and formulate a solution. He then opened the floor for discussion.

Dr. Wells agreed that the meeting was successful and, on behalf of the task force, reported that they look forward to moving ahead and developing solid recommendations.

Dr. Wilson expressed his optimism in finding a solution, due primarily to the fact that such a large amount of the information necessary for the project was available at this first meeting. He stated that he had anticipated a long-term effort by staff to gather the information necessary to analyze and remedy the situation. Dr. Calabresi further noted that this was a very positive sign, commending the staff's strong support in formulating the problem and providing assistance in implementing a solution. He recommended that the task force focus on this matter and expressed his confidence that they would formulate some positive solutions by September.

All were in favor of the motion to approve Dr. Calabresi's report.

Information and Cancer Control

Dr. Erwin Bettinghaus, substituting for Ms. Marlene Malek, reported on the subcommittee's consideration of two issues during their meeting.

The subcommittee agreed unanimously not to recompete the current CIDAC contract and endorsed an electronic version of Cancergrams to be distributed on CancerFax, thereby resulting in a yearly cost savings of $600,000.

Following some discussion, the subcommittee approved a concept for a cooperative agreement for a telephone service to distribute PDQ information to health professionals. Improved use of PDQ will be evaluated for its ability to serve the health professional community, especially those serving minority and other underserved populations.

The report of this subcommittee was unanimously approved.

Interactions With Voluntary Organizations Subcommittee Report

Dr. Walter Lawrence explained that this subcommittee held an all-day meeting on January 27, 1993, at which the following three issues were discussed: 1) national planning conference to foster communication between the NCI and voluntary organizations; 2) the ASSIST program; and 3) coordination of statistics and epidemiology between the NCI and the American Cancer Society.

Communication With Other Organizations

Dr. Lawrence reported that the first item on this subcommittee's agenda was the organization of a national planning conference with outside health organizations to develop a plan for better communication with and understanding of these groups. Representatives from outside voluntary health organizations had attended the January 27th meeting and with their input, Dr. Lawrence stated, the subcommittee identified 20 voluntary organizations, primarily non-Government, volunteer-driven organizations with a focus on cancer, to invite to the national conference. He explained that 6 of these 20 organizations were chosen to form a planning group to develop an agenda and a plan for the conference, with the hope of fulfilling the expressed needs of the organizations.

Dr. Lawrence asked for a motion to proceed with a half-day planning meeting on April 19, 1993, consisting of the co-chairpersons—Dr. Lawrence and Ms. Mayer—and representatives of broad-based organizations, including: the American Cancer Society; the National Coalition for Cancer Survivors; the Candlelighters; the National Alliance of Breast Cancer Organizations (NABCO); and Us Too. He added that if the motion was approved, the planning group could present a tentative agenda first to the group that met on January 27th and then to the NCAB in May. If this could be accomplished, Dr. Lawrence explained, a meeting of approximately 20 organizations could be held in early or mid-1994.

Ms. Mayer stressed that the important part of this motion is the need to meet with the smaller planning group. The small group, she added, would make recommendations about better communication with the NCI, which may or may not include a national conference.

Dr. Lawrence recognized the benefit of Ms. Mayer's point. He added that his commitment to the idea of a national conference led him to overlook the fact that some subcommittee members felt that other mechanisms could better accomplish their goal. Dr. Lawrence moved for the NCAB to conduct a national conference on collaboration between the NCI and voluntary health organizations to include in the planning process representatives from several volunteer-driven, non-Government organizations with a primary focus on cancer. He explained that he had reworded his motion at the last minute to include an emphasis on the planning process rather than simply to hold a national conference.

Dr. Calabresi stated that he believes the general idea is a good one, but he expressed concern about how the planning organizations are to be selected and the short lead time to plan a conference for April 19, 1993. Dr. Lawrence clarified that a small planning meeting would be held on April 19th, not the national conference. He explained that the subcommittee arbitrarily chose the planning groups, based on their interests and constituencies.

Dr. Salmon expressed concern about being exclusionary in the planning phase, noting his assumption that there were other organizations present at the January 27th meeting that were not invited. He asked whether the attendees complained about the choice of groups or seemed satisfied. Dr. Lawrence responded that everyone seemed to agree with the chosen groups and the idea of a small planning meeting. He added that it is not possible to pay for the travel costs of all guests who might come to the national conference or open meeting. Dr. Salmon replied that he did not realize there were funding implications. Dr. Lawrence commented that about half of the organizations have representatives in Washington, DC, and, therefore, require little funding. He added that the planning meeting would be open and that a mechanism would be developed to address Dr. Salmon's concern about allowing others to attend.

Dr. Calabresi suggested inviting the chosen organizations, but using an open meeting format to allow others to sit in the audience. Dr. Lawrence stated that it is difficult to plan an agenda with a large group, but that this suggestion is a good compromise. Dr. Salmon suggested that the designated planning group sit around a center table, with others welcome to sit in the room to listen, a style similar to that used for NCAB meetings. Dr. Calabresi expressed complete agreement with Dr. Salmon.

Dr. Sigal stated her concern about whether a conference is the best vehicle to use to achieve better communication. She expressed hope that the small meeting in April will actually serve as a forum to discuss whether the conference is needed, before planning begins. Dr. Lawrence stated that if the NCAB approves the motion for the planning meeting, it is essentially granting approval for a national conference, should the planning group decide to move in that direction. If the NCAB as a whole feels that the conference is a reasonable solution to a significant problem, he continued, then the planning meeting should take place.

Following up on Dr. Sigal's comment, Dr. Salmon suggested that the subcommittee consider other meetings, video conferencing, or a newsletter to foster ongoing communication. Since national conferences are extremely expensive and take place only once, he wondered whether large conferences would help to accomplish the stated goal. Dr. Lawrence stated that the purpose of the April 19th meeting is to develop a long-range process and plan with outside organizations. The proposed motion, he continued, is a two-step process for accomplishing Dr. Salmon's suggestion of fostering improved, ongoing communication.

Mrs. Bynum asked for clarification on whether the motion was to hold only a planning meeting or to hold a meeting with the intent of planning a national conference. Dr. Lawrence explained that he sought approval to hold a meeting with the purpose of planning a national conference. Dr. Chan asked whether the Board would be voting for the planning committee first and then the national conference later, or both. Dr. Becker suggested that Dr. Lawrence restate the motion.

Dr. Lawrence restated the motion to approve a national conference to be held in 1994, which would focus on collaboration between the NCI and voluntary organizations, and would include in the planning process voluntary, non-Government, health organizations with a primary focus on cancer.

Dr. Salmon recommended that the motion be divided, so that the initial planning meeting is approved first. Dr. Calabresi announced that the Board would vote on Dr. Lawrence's motion as proposed. If approved, there would be a planning meeting and a national conference, if the planning meeting members so decided. If not approved, Dr. Calabresi said, the Board could then put forward a divided motion. Mrs. Bynum counted five in favor of the motion, seven against, and one abstention.

Dr. Lawrence made a second motion to approve a planning group comprised of representatives of voluntary, non-Government, cancer-focused health organizations to meet to study means of developing better collaboration between the NCI and voluntary organizations. The Board unanimously approved this motion.

The ASSIST Program

Dr. Lawrence reported on the other agenda items of the January 27th subcommittee meeting, noting that the committee had assessed the collaborative effort with the ASSIST program. Dr. Lawrence noted that the budget of the ASSIST program was not considered, and commented that presentations by staff of NCI and the American Cancer Society were excellent. The committee discovered problems in collaboration between the national coalition

of the NCI and the American Cancer Society and local sites. Discussions at the subcommittee meeting between national representatives and guests from the local sites led to the formulation of solutions and a general sense of improved communication.

Dr. Lawrence commented that the committee was impressed with the ASSIST program and felt that tobacco control should be a major agenda item for a future NCAB meeting. He noted that, despite his opinion that the issue should be presented soon, the committee as a whole decided that it should be deferred until 1994, after the data from the COMMIT study are in and the implementation of the ASSIST program can also be discussed.

Coordination of Statistics and Epidemiology Between the NCI and the American Cancer Society

Regarding the last agenda item of the January 27th subcommittee meeting, Dr. Lawrence stated that the committee heard excellent presentations from Brenda Edwards from NCI and Clark Heath from the ACS about better collaboration between these organizations.

Dr. Lawrence added that everyone in attendance was impressed with the NCI and ACS programs and that the participants and the approximately 35 guests, who were made ad hoc members of the subcommittee, were pleased with the outcome of the meeting. Dr. Lawrence concluded that the subcommittee feels they are making progress.

The Board unanimously approved the Interactions With Voluntary Organizations Subcommittee report.

Minority Health, Research, and Training Subcommittee Report

Mrs. Zora Brown announced that in this subcommittee's brief meeting, Dr. Cairoli presented an update on the progress of the National Institutes of Health Subcommittee on Minority Recruitment on institutional training grants. Dr. Cairoli indicated that 16 institutions had responded to a survey questionnaire on their experiences and procedures for minority recruitment institutional training grants during fiscal year 1992. Major findings of the survey included 100 percent compliance in providing a recruitment plan with 9 percent of the plans judged to be unacceptable. Revised recruitment plans are reviewed by internal staffs for all Institutes, except NCI and NIAID, which return them to their review committees. The National Institute of General Medical Sciences (NIGMS) and NIEHS are unique in providing formal council discussions of their plans. During the past 5 years, almost 100 percent of minority recruitment plans submitted to the NIH have been evaluated to be acceptable for these training grants. NIH is currently drafting guidelines and review criteria to assess the success of these plans.

Mrs. Brown reported that Dr. Lemuel Evans of the Comprehensive Minority Biomedical Program had presented a concept for subcommittee review entitled "Minority Enhancement Awards" (MEAs). The general research objectives of this initiative would include, but are not limited to, evaluation of smoking behavior in minority youth, study of communication strategies for presenting information to minorities about cancer and its

prevention, investigation of patient perspectives of cancer risk, design and evaluation of interventions to minimize and prevent distress in minority patients with cancer, development of pilot studies for minority clinical prevention trials, and psychosocial studies of perceptions of cancer risk in minorities.

Mrs. Brown indicated that the subcommittee members engaged in an extensive discussion about suggestions and changes to this submission. She reminded the Board that copies of the concept were distributed to all members, and noted that the subcommittee voted unanimously to approve the concept with their recommended changes. Mrs. Brown announced a motion for the Board to approve the plan to implement this concept through a Request for Applications.

Regarding the motion, Mrs. Bynum reminded Board members that the MEA concept represents a replacement for the previous cancer control outreach in minority populations awards that were first awarded as supplements to cancer center grants. She added that this concept will replace that initiative and will be funded out of the RPG line.

The Board unanimously approved the motion to implement Minority Enhancement Awards.

On behalf of the NCI, Mrs. Bynum expressed her appreciation to Dr. Cairoli and his staff for examining the recruitment plans. Mrs. Bynum pointed out that the NCI represented the 29 percent of the 0 to 29 percent range of unacceptable plans submitted to the NIH. She noted that the assessment phase will be of particular interest to the NCAB.

The Board unanimously approved the Minority Health, Research, and Training Subcommittee report.

Planning and Budget Subcommittee Report

Dr. Erwin Bettinghaus reported that this subcommittee/task force met on the previous day to discuss grants to foreign institutions or investigators and the bypass budget. Subcommittee members approved the data provided by Mr. Philip Amoruso on foreign grants. Dr. Bettinghaus stated that 1993 estimates of grants awarded to foreign institutions or investigators constituted less than 1 percent of the total and, therefore, subcommittee members agreed to Dr. Broder's request that they no longer discuss this issue at NCAB meetings.

This subcommittee/task force agreed to provide assistance to the Institute on the formulation of the 1995 bypass budget, which will be published in September of 1993. First, it will review the current bypass budget and highlight areas requiring further clarification. Second, it will hold a meeting no later than April 15, 1993, to provide direct assistance to Dr. Ihde and his staff, who are responsible for the preparation of this document. Third, this subcommittee/task force will forward recommendations to the NCAB for review, format, and approval. In order to prepare for the April subcommittee meeting, Dr. Bettinghaus requested that members send their comments and suggestions to either Mrs. Bynum, Cherie Nichols, or himself within the next 3 to 4 weeks.

Dr. Bettinghaus concluded his report by noting that the minutes of this subcommittee meeting had not been completed for distribution prior to the NCAB meeting, but would be sent to members promptly.

Dr. Broder expressed his appreciation to NCAB members for their advice and assistance in meeting the deadline for the 1995 bypass budget.

The Board unanimously approved the Planning and Budget Subcommittee report.

Program Project Task Force Report

Dr. Wells reported that this task force met on the previous day with three items on its agenda: 1) evaluation of the process of peer review; 2) evaluation of the means by which application scores are ranked; and 3) designation of special areas of emphasis that could be used to decide funding for grants.

Dr. Wells stated that one source of information was the article on peer review of P01 applications and the place of POIs in the NCI portfolio written by Dr. Broder for *Cancer Research*. It generated several questions regarding peer review, the funding process and evaluation of grants, and the interdigitation and comparative analysis of R01 grants. Also questioned was the role of interactive RPGs and whether or not they could be a mechanism for funding previously structured P01 grants. Dr. Wells announced that a report is forthcoming on the future of these grants. He said that this group will meet again at least once before the next NCAB meeting and will report to the Board in May.

The Board unanimously approved the Program Project Task Force report.

Women's Health and Cancer Subcommittee Report

Mrs. Brenda Johnson reported that this subcommittee heard two presentations on breast cancer research. Mr. John Hartinger reviewed the NCI bypass budget request for breast cancer research and trends in actual planning. He reported that spending for breast cancer research in fiscal year 1992 was approximately $145 million. The bypass request for FY 1994 is $448 million, or 14 percent of the total $3.2 billion budget. Of this, $73.5 million would be allocated to breast cancer research supported by other NIH components.

Regarding the $210 million appropriated to the Department of Defense for breast cancer, Mrs. Johnson stated that the money did not come from the NCI budget, and the NCI does not yet know how these funds will be used. The Army has contracted with the Institute of Medicine (IOM) to advise on priority areas of research and the conduct of peer review for the award of these funds, and several meetings will be held in the next few months. General Travis, the responsible official for the Army, and Dr. Cassells, the IOM study director, will address the President's Cancer Panel Special Commission on Breast Cancer meeting in Washington, DC, on February 23, 1993. Mrs. Johnson stated that the subcommittee will hear an update on the IOM study in May.

Mrs. Mary Jo Kahn of the Virginia Breast Cancer Foundation addressed the subcommittee on behalf of the National Breast Cancer Coalition. Mrs. Johnson reported that the Coalition is developing its recommendations for the breast cancer section of the 1995 bypass budget. She noted that Mrs. Kahn reiterated the urgency and commitment felt by breast cancer advocates; specific areas of concern include early detection and prevention of breast cancer. Mrs. Johnson pointed out that although Mrs. Kahn stated that she is not opposed to the tamoxifen trial, she said she prefers to see studies specific to the true causes of breast cancer at the cellular level. Mrs. Kahn indicated the strong interest of the Coalition in working with the NCI and in participating with its advisory committees.

Mrs. Johnson reported that the subcommittee considered whether to develop specific input regarding the FY 1995 breast cancer bypass request for the Budget and Planning Subcommittee. She reported that Dr. Bragg had noted the overlapping membership between the subcommittees and had offered to represent concerns about breast cancer.

Mrs. Johnson said that Dr. Peter Greenwald had then described some of the NCI-funded breast cancer prevention research. Dr. Broder mentioned at the meeting that he had talked with Dr. Francis Collins, the incoming director of the National Center for Human Genome Research, who has stated his commitment to making the pursuit of the breast cancer gene a high priority. Dr. Broder also reported that breast cancer vaccines, while not ready for clinical application, still hold promise for future use to prevent recurrence of breast cancer and might someday be used for primary prevention in high-risk women.

The Board unanimously approved the Women's Health and Cancer Subcommittee report.

XIV. NEW BUSINESS

Mrs. Bynum called Board members' attention to a sheet in their notebooks marked "Guidelines for NCI Staff in Negotiating Desirable Adjustments in Grants." She explained that this guideline requires that each year, the NCAB delegate to the NCI grants management and program staff, the authority to make adjustments in grants during the award negotiation process. Mrs. Bynum asked for a motion for approval, and Board members voted unanimously in favor of the motion.

Mrs. Bynum concluded by reminding members to submit signed conflict of interest and new standards of conduct forms either to herself or Dr. Gray. Dr. Calabresi then asked for any other items of new business.

Dr. Sigal expressed her concern about the reliability of cancer cost data and requested that a subcommittee be appointed to examine the economics of cancer. Dr. Calabresi replied that he would consider Dr. Sigal's request. He stated that this is an important topic, but explained that he would like to avoid appointing too many committees. Perhaps, Dr. Calabresi commented, this topic could be incorporated into an existing committee's agenda. Regarding

Dr. Sigal's concern, Dr. Bettinghaus commented that policy decisions probably would not change if the reliability of data improved.

Dr. Day suggested that future Board meetings include a series of presentations on environmental and occupational factors in the causation of cancer by intramural or extramural staff. He noted that electromagnetic fields (EMF) is one of the most important issues in this area because of the use of hydropower in long transmission distances. Cellular telephones, he said, are an additional related problem. The Board should also be apprised, he continued, of new information such as that now available on the potentiation factors between hepatitis and aflatoxin. He suggested that the Board ask the National Institute for Occupational Safety and Health (NIOSH) and the National Institute of Environmental Health Sciences (NIEHS) to assist in making a major presentation or series of presentations at future meetings. Dr. Day said he believes the National Cancer Program will continue to receive criticism for its lack of emphasis in this area.

Dr. Adamson responded that the National Cancer Program does, indeed, focus on environmental health and occupational issues. He reminded Dr. Day that a program review of cancer etiology, including the Agriculture Health Study, was presented at the December NCAB meeting, and that Dr. Becker had presented the Subcommittee on Environmental Carcinogenesis' report on EMF at a previous meeting. Dr. Adamson added that the Subcommittee on Environmental Carcinogenesis is examining additional topics of discussion for future meetings.

Dr. Salmon requested that a single presentation on electromagnetic fields be given at a future Board meeting. Dr. Adamson answered that an entire subcommittee report had been devoted to this subject at a recent meeting, and that other previous subcommittee reports had concerned heterocyclic amines and occupational studies. He noted that these presentations could be made to the Board as a whole, rather than to subcommittees. Dr. Broder responded that because of the importance of the problem and the new membership on the NCAB, future Board presentations will focus on environmental health and occupational issues. He mentioned possible topics of discussion, including rehabilitation issues in cancer, and environmental and occupational research programs in the NCI, NIH, and other sister agencies.

Dr. Salmon requested that copies of the subcommittee report on electromagnetic fields be distributed to Board members. Dr. Adamson answered that copies of this report will be distributed.

Dr. Broder added that the Board will be apprised of an emergency study on cellular phones. He commented that the NCI considers environmental and occupational carcinogenesis an important issue and part of its total research agenda.

Dr. Day recommended that the Board consider presentations on environmental and occupational carcinogenesis on a regular basis. Dr. Calabresi reminded Board members to suggest any topics of interest to himself or Mrs. Bynum. He added that the agenda committee can help to include as many items of interest to the agenda as possible.

XV. ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 85th National Cancer Advisory Board meeting at 12:45 p.m.

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Date Dr. Paul Calabresi, Chairman