

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

**Summary of Meeting  
February 27-28, 1996**

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



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**Lists of Attendees for:**

**NATIONAL CANCER ADVSORY BOARD (NCAB) MEMBERS  
PRESIDENT'S CANCER PANEL MEMBERS  
EX OFFICIO NCAB MEMBERS  
MEMBERS, EXECUTIVE COMMITTEE, NATIONAL CANCER INSTITUTE, NIH  
LIAISON REPRESENTATIVES**

**NCAB MEMBERS**

- Dr. Barbara K. Rimer (Chairperson)

- Dr. Frederick F. Becker
- Dr. J. Michael Bishop
  - Dr. Richard J. Boxer
  - Mrs. Zora K. Brown
  - Dr. Kenneth K. Chan
  - Dr. Pelayo Correa
  - Dr. Robert W. Day
  - Dr. Kay Dickersin
  - Mrs. Barbara P. Gimbel
  - Dr. Alfred L. Goldson
  - Mrs. Marlene A. Malek
  - Ms. Deborah K. Mayer
  - Dr. Sydney Salmon
  - Dr. Philip S. Schein
  - Dr. Ellen V. Sigal
  - Dr. Vainutis K. Vaitkevicius
  - Dr. Charles B. Wilson (absent)
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### **PRESIDENT'S CANCER PANEL**

- Dr. Harold P. Freeman (Chairperson)
  - Dr. Paul Calabresi
  - Ms. Frances M. Visco
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### **ALTERNATE EX OFFICIO NCAB MEMBERS**

- Dr. Alison Martin, FDA
  - Ms. Lynn Jenkins, NIOSH
  - Dr. Marilyn A. Fingerhut, NIOSH (absent)
  - Capt. Bimal C. Ghosh, DOD
  - Dr. Hugh McKinnon, EPA
  - Ms. Rachel Levinson, OSTP (absent)
  - Dr. Lakisma C. Mishra, CPSC
  - Dr. Gerald Poje, NIEHS (absent)
  - Dr. Paul Hoffman, DVA
  - Dr. P.C. Srivastava, DOE
  - Dr. Ralph E. Yodaiken, DOL
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### **MEMBERS, EXECUTIVE COMMITTEE, NATIONAL CANCER INSTITUTE, NIH**

- Dr. Richard Klausner, Director, National Cancer Institute
- Dr. Alan Rabson, Deputy Director, National Cancer Institute
- Dr. Edward Sondik, Associate Director, Strategic Planning
- Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
- Ms. Maryann Guerra, Associate Director for Intramural Administrative Management
- Dr. Faye Austin, Acting Director, Division of Cancer Biology; Chairman, Extramural Advisory Board
- Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
- Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
- Dr. Marvin Kalt, Director, Division of Extramural Activities
- Dr. Philip Pizzo, Acting Director, Division of Clinical Sciences
- Dr. Robert Wittes, Director, Division of Cancer Treatment, Diagnosis, and Centers

- Dr. George Vande Woude, External Advisor, Division of Basic Sciences; Director, Advanced BioScience Laboratories, Inc., NCI-Frederick Cancer Research and Development Center
- Dr. Claude Klee, Chairman, Intramural Advisory Board, Board of Scientific Counselors
  - Dr. Martin Abeloff, External Advisor and Co-Chairman Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology Center
  - Dr. David Livingston, External Advisor, Chairman of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
  - Dr. Edward Harlow, External Advisor and Co-Chairman, Basic Sciences Subcommittee B of the NCI Intramural Board of Scientific Counselors; Member, Massachusetts General Hospital
  - Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics, Acting Director Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center
  - Mrs. Iris Schneider, Executive Secretary, Asst. Director for Program Operations and Planning
  - Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel
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### **LIAISON REPRESENTATIVES**

- Dr. John Currie, American Association for Cancer Education, Inc.
  - Dr. Marc E. Lippmann, American Association for Cancer Research (absent)
  - Dr. Margaret Foti, American Association for Cancer Research
  - Dr. Robert Martuza, American Association of Neurological Surgeons
  - Dr. John Laszlo, American Cancer Society (absent)
  - Ms. Kerrie B. Wilson, American Cancer Society
  - Ms. Elaine Locke, American College of Obstetricians and Gynecologists
  - Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists (absent)
  - Dr. Bernard Levin, American Gastroenterological Association (absent)
  - Dr. Edward P. Gelmann, American Society of Clinical Oncology
  - Dr. John Glick, American Society of Clinical Oncology
  - Ms. Julie Taylor, American Society of Clinical Oncology
  - Dr. Stanley Order, American Society of Therapeutic Radiologists (absent)
  - Dr. Edwin A. Mirand, Association of American Cancer Institutes
  - Dr. Robert W. Frelick, Association of Community Cancer Centers
  - Mr. James Kitterman, Candlelighters Childhood Cancer Foundation (absent)
  - Mr. Thomas Brandt, Intercultural Cancer Council
  - Ms. Melinda Friend, Leukemia Society of America, Inc.
  - Ms. Dorothy J. Lamont, National Cancer Institute of Canada (absent)
  - Dr. J. David Beatty, National Cancer Institute of Canada (absent)
  - Dr. Tracy Walton, National Medical Association
  - Dr. Eve I. Barak, National Science Foundation
  - Dr. James Brown, National Science Foundation
  - Ms. Mary Baroni, Oncology Nursing Society (absent)
  - Ms. Roberta Strohl, Oncology Nursing Society
  - Dr. Jeffery Norton, Society of Surgical Oncology, Inc. (absent)
  - Dr. Marston W. Linehan, Society of Urologic Oncology (absent)
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### **CALL TO ORDER AND OPENING REMARKS**

**Dr. Barbara Rimer called to order the 97th meeting of the National Cancer Advisory Board (NCAB). Dr. Rimer introduced guests representing several cancer education and research associations and institutions as well as Federal agencies involved in cancer-related issues. She welcomed the members of the public and invited them to submit in writing any comments regarding items discussed during the meeting. Comments should be submitted**

within 10 days of the meeting to Dr. Marvin Kalt, Executive Secretary of the Board.

Dr. Rimer referred to the confirmed meeting dates for 1996, 1997, and 1998, and asked Board members to report any conflicts with future meeting dates as soon as possible. She indicated that 3-day meetings have been scheduled, but they are anticipated to last only 2 days.

Dr. Rimer called for approval of the minutes of the November 28-29, 1995, meeting. The motion was seconded and the minutes were approved.

Dr. Rimer announced that the meeting agenda was full and asked that all members be in attendance for voting. She also asked that any grant applications to be discussed be given to Dr. Kalt before or during the morning break. Dr. Rimer announced that subcommittee meetings would be held during and following lunch, as well as at the close of the afternoon session.

Dr. Rimer thanked all the Federal employees for their sacrifices during the Government furlough. She thanked Mr. Paul Van Nevel for his new "Heads Up" memos and Dr. Philip Pizzo for serving as a liaison to the National Institute's of Health (NIH) Director's Panel for Clinical Research.

Dr. Rimer welcomed the newest Board member, Dr. Richard Boxer, who was appointed in the fall. She then congratulated two Board members that had been honored. Dr. Fred Becker was awarded the Princess Thule award, a medal of science from Thailand, and Dr. Kay Dickersin was recognized by the City of Baltimore for the Women's Hall of Fame.

Dr. Rimer noted Dr. Robert Day's announcement to step down as head of the Fred Hutchinson Cancer Center in 1997, and that he has already been drafted to head the Special Actions Committee as Dr. Salmon departs the Board.

Dr. Rimer highlighted some of the activities that Board members had been involved in since the last NCAB meeting. She then reviewed a list of presentations scheduled for the day's Board meeting.

Dr. Rimer introduced Dr. Harold Freeman, Chairperson of the President's Cancer Panel, to report on the recent activities of the President's Cancer Panel.

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## **REPORT OF THE PRESIDENT'S CANCER PANEL**

Dr. Freeman announced that he would be sharing with the Board some of the conclusions of the President's Cancer Panel's explorations over the last 2 years. The Panel explored diverse topics, including socioeconomic status and its implications for cancer; relationships between culture and cancer; the Federal Trade Commission's cigarette test determining tar, nicotine, and carbon monoxide content; lung cancer; avoidable causes of cancer; the ramifications of the human genome project; AIDS neoplasms; progress against leukemia; and the "Information Superhighway."

Dr. Freeman highlighted the estimation that two-thirds of cancers are attributable to the behaviors of individuals—primarily smoking and inadequate/inappropriate diet—suggesting that more than half of cancers can be prevented. He indicated that this information provides a lead for activities that should be undertaken. For example, the Nation has taken a stance against tobacco use. The scientific community must maintain that stance wholeheartedly and support the efforts of the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), and state and local jurisdictions that are acting to limit access to tobacco, particularly to young people. More important, the Panel feels that efforts to arm children with knowledge about smoking and health must be improved.

Dr. Freeman emphasized that it is essential to encourage actively future generations to take responsibility for their own health and well-being through health promoting behaviors and through the ability to assess the

effects of their behaviors on their health. This recommendation is consistent with the recommendation of the President's Cancer Panel and the Subcommittee to Evaluate the National Cancer Advisory Program (SENCAP) report to apply the scientific knowledge that has been gained. Important first steps are the development of better health-based curricula for young people and the improvement of communication within the scientific community and among the American public to reinforce health-related lessons.

In addition, Dr. Freeman stated that training needs at all educational levels must be assessed to determine whether future researchers and physicians are being equipped with knowledge that will ignite the desire for a lifetime dedication to cancer research. Graduate level curricula must be structured to include the training necessary to respond to the evolving needs of basic, clinical, and population-based research.

Dr. Freeman noted that informatics as a tool is here to stay, and that research training must provide the skills needed to interface in tomorrow's world. Further, the Panel feels that the way in which health-related data is collected and provided must be reexamined to assure that baseline assumptions about needed data are consistent and valid. As more scientific knowledge is compiled, its implications and those of technology on health care and the welfare of individuals must be remembered. As the Panel has emphasized before, the National Cancer Institute (NCI) cannot afford to underestimate the impact of the rapid increases in genetic knowledge and other future scientific developments in many areas, including employment, insurance, and access to health care. The Panel maintains that the administration of genetic tests should be limited to the research arena until employers, insurers, and health care providers have a better understanding of its implications, and until the psycho-support necessary to cope with an adverse genetic finding becomes an integral part of the health care system.

Finally, Dr. Freeman stated that the Panel continues to assert that clinical research is the key support and backbone of the National Cancer Program. The Cancer Centers, Cooperative Groups, and other programs are the training grounds for future researchers, but they are also the arena in which research becomes standard treatment.

Dr. Freeman concluded that it is essential to educate all Americans about the value of clinical research and to cultivate new physicians and researchers.

Dr. Rimer thanked Dr. Freeman for his presentation. After determining that there were no questions or comments from the Board, Dr. Rimer introduced Dr. Richard Klausner, Director of the National Cancer Institute.

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## REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. Klausner commended the staff of the NCI and other Federal employees for their good spirit and commitment during the Government furlough. Dr. Klausner recognized the impact of the furlough on individuals wanting to get their important work done, and the difficulties they continue to face in catching up with the enormous amount of work. Dr. Klausner added that, with the resolution of the furlough, the NIH received a generous increase in the budget of almost 5.8 percent.

Dr. Klausner then moved to a discussion of the important and exciting discoveries that have continued to increase our understanding of the fundamental nature of the cancer cell. He listed several discoveries that have occurred since the last NCAB meeting, including the full identification of the second breast cancer susceptibility gene, BRCA2, and the identification by Scott Kearn and colleagues at Johns Hopkins of the first specific susceptibility gene for pancreatic cancer, DCP-4, which is associated with more than 50 percent of pancreatic cancers.

Dr. Klausner announced that just last week, NCI-funded researchers from the Jefferson Cancer Center, led by

Dr. Carlo Croce, identified a general cancer susceptibility gene called FHIT, or fragile site in histidine triad protein. This gene appears to be abnormal or lost in the majority of lung cancer cases, approximately 50 percent of stomach, esophageal, and colon cancer cases, and 30 to 40 percent of breast cancer cases, as well as in some ovarian and cervical cancer cases. The gene was first identified in an Italian American family in 1979 with inherited renal cell cancers; it is located at chromosome 3p14.2, the most fragile site in the human genome. The FHIT gene is highly expressed in epithelial cells that are directly exposed to the environment.

Dr. Klausner indicated that the FHIT gene was noted to be 70 percent identical to an enzyme, a diadenosine tetraphosphate asymmetric hydrolase, found in a simple fission yeast (*Schizosaccharomyces*). This enzyme may work by changing levels of a nucleotide, AP4A (adenosine tetraphosphate adenosine), which may be an intracellular signal that controls cellular responses to damage. Dr. Klausner explained that this is an exciting discovery, because the enzyme has known products in known metabolic pathways and may result in abnormal signalling because of specific changes that scientists may be able to alter.

Dr. Klausner emphasized that the engine of discovery keeps advancing and that early ideas about therapeutic maneuvers based on discoveries are beginning to develop. He explained that discovering a cancer predisposition gene means the beginning of understanding pathways, and the understanding of pathways will help produce specific ideas about how to intervene. Dr. Klausner indicated that molecular diagnostics holds great promise for detection of risk for diagnosis, stratification response to therapy and prognosis, and clinical trials. Extensive clinical trials systems using biologic correlations are demonstrating the utility of such approaches, and these will be a priority for many studies.

Dr. Klausner commented that examples of the use of molecular diagnostics abound. The recent identification of microsatellite instability and the recognition that mononucleotide "runs"--runs of the same DNA base--are the most sensitive measure of a type of DNA instability that characterizes many tumors are leading to clever new diagnostic approaches, at least in the laboratory. These approaches include the newly described sensitive and efficient detection of transformed cells in the urine for bladder cancer recently reported by Dr. David Sidranski.

Dr. Klausner announced that he has asked Dr. Arnold Levine from Princeton to oversee a working group, scheduled to meet soon for a weekend retreat, to advise the NCI on how it can best capitalize on the enormous potential of developmental diagnostics and stimulate the development and application of new technologies in this area. Dr. Klausner and Dr. Levine discussed the "information superhighway," and noted that, although molecular diagnostics is fairly primitive, it is time to take proactive steps to begin doing things that may now seem like science fiction.

Dr. Klausner explained that the NCI's priorities for this year and the future are twofold. They are (1) to use its budget, mechanisms, and the creativity of its community to maintain the engine of discovery, and (2) to assure that those discoveries benefit patients.

Dr. Klausner indicated that the NCI can work towards both of these goals through the judicious use of its budget. Dr. Klausner presented his first slide and explained that the NCI budget for fiscal year 1996 is \$2,251,000,000. He noted that this year, for the first time, the NCI will be spending over \$1B in the Research Project Grants (RPG) pool. Dr. Klausner stated that the Cancer Centers received an increase of approximately \$11M, allowing the NCI to fund a variety of programs, including two special initiatives.

In one initiative, for which \$3M to \$6M have been set aside for administrative supplements, applications from all NCI Cancer Centers are being invited to propose the development of programs in cancer genetics, based upon the expertise and special characteristics of each of the Centers. The initiative has two aspects: one is to further basic research in this area, and the other is to establish programs in training and education aimed at genetic counseling. There are only 1,400 genetic counselors in this country, and few of them are specifically trained in oncology. The NCI is looking for creative proposals to either expand existing programs or to create new programs to train primary care practitioners, nurses, social workers, psychologists, and health care educators in cancer genetics.



The second initiative, for which \$2M to \$5M has been set aside for administrative supplements, involves asking the Cancer Centers to produce applications in the area of AIDS malignancies. Malignancies complicate the course of AIDS in approximately 30 percent of cases. This represents an important opportunity for the cancer program to learn about aggressive cancers in the setting of immune stimulation/immune deficiency, as well as those specifically associated with viral causes and viral progression.

Dr. Klausner indicated that \$15M has been added to the Clinical Cooperative Groups budget line. Dr. Klausner explained that the NCI's clinical trials system is the backbone of its ability to translate discovery for the benefit of patients, and that this additional funding increases approaches for informatics, opportunities to do correlative studies, and the percentage of recommended funding.

The budget for intramural research is \$405M, which represents 18 percent. Dr. Klausner explained that this figure is an accurate measure of what the intramural program spends, plus about \$20M to \$25M from additional contracts that are not at the intramural line. Dr. Klausner noted that much time has been spent establishing cost management principles and zero base budgeting. For the first time, the budgets of all of the laboratories and branches are using cost management principles. With these measures, real savings are seen in the intramural line compared with the previous real expenses.

Dr. Klausner referred to a new intramural program booklet that states the principles of the organization of the intramural program, defines principal investigators and lab chiefs and delineates their responsibilities for oversight and mentorship, and describes the expectations and criteria by which individuals will be reviewed. Dr. Klausner recommended that the Board read this booklet, which was reviewed by the Intramural Advisory Board.

Dr. Klausner discussed the NCI goal of dealing with core problems, including the lack of opportunity for individuals to do research as indicated by the low success rates, the low payline, and the lack of money available for investigator-initiated research. Dr. Klausner described the changes that have been made to free up money. Dr. Klausner's next slide showed the increases in paylines for 1996 compared with 1995. R01 Individual Investigator Initiated Grants moved from the 15th percentile to the 23rd percentile; P01 Program Project Grants moved from a priority score of 134 to 140; First Independent Research Support and Transition (FIRST) awards increased from the 27th percentile to the 30th percentile; the priority score for small grants moved from 180 to 200; and, finally, R21 Exploratory Grants moved from the 21st to the 25th percentile. Dr. Klausner added that these increases were based on prediction of the budgets for the next few years, and that it is hoped this range can be sustained. He acknowledged the sense of commitment on the part of the Congress to the NIH.

In addition to raising the payline, the NCI is working on situations in which paylines are not reached. Dr. Klausner recognized the difficulty of the amendment process for grants, especially when they are close to the payline and an amendment is likely ultimately to be funded. The long wait for funding is destabilizing and demoralizing to researchers and difficult for the study sections that have been overwhelmed with reviewing amendments rather than new grants. Dr. Klausner explained that this is a particular problem for patient-oriented research; those grants do not do well, relatively, on the first submission, although they do well on subsequent submissions. There is a large drop out of patient-oriented research proposals between the first submission and the subsequent submission, possibly because the investigators become discouraged, and because they are expected to generate income from seeing patients. Also, Dr. Klausner noted that it takes much effort to organize and submit a grant for patient-oriented research, and that the opportunity is lost by waiting a couple of years.

Dr. Klausner indicated that the NCI initiated the process of Accelerated Executive Review (AER) to deal with these issues. If an individual is doing patient-oriented research, using the Nathan committee definition of the term, and is within 10 percentile points of the payline (i.e., up to the 33rd percentile), the Institute will send a letter requesting a five-page report responding point by point to the review. New data, either in press or published, can be submitted. Within 1 month, the executive committee will review the report and determine whether or not to fund these individuals. AER does not guarantee funding, but the accelerated mechanism sends the message that the NCI is interested in patient-oriented research, recognizes the problems, and is willing

to be responsive to them.

Dr. Klausner announced that money has been set aside, based upon the number of grants predicted to be within this percentile, for AER to fund 40 to 50 percent of submitted proposals. However, if more grant proposals successfully respond to the concerns, "exceptions" money is available to fund more grants. Dr. Klausner emphasized that accelerated review is not just for patient-oriented research. AER applies to all unamended R01s, but R01s must be within 4 percentile points (i.e., up to the 27th percentile). Patient-oriented research only needs to be within 10 percentile points because of its particular problems and the need to send a strong message of support to individuals conducting this research.

Dr. Klausner noted that there have been productive discussions with professional societies, especially the American Society of Clinical Oncology (ASCO), about active mentorship of young individuals trying to do patient-oriented research. ASCO has been enthusiastic about helping these individuals respond to the AER. Dr. Klausner added that the NCI is also increasing the opportunities for training across many of the categories. He presented a slide showing that the total number of trainees funded by the NCI will go up from 1,666 to 1,733.

Dr. Klausner mentioned a proposal discussed at the Planning Subcommittee for a new honorific award, the Howard Temin award, aimed at attracting young M.D.s or Ph.D.s to a career in cancer research and giving them stable funding to bridge the critical period between leaving a mentored position and beginning an independent position. The NCI will begin with 10 5-year awards, covering up to \$75,000 in salary and \$50,000 for research expenses per year. Awardees must have completed 3 years of mentorship and can stay for up to 3 more years in a mentored lab, before moving to an independent position to complete their 5-year award. Dr. Klausner expressed the NCI's excitement about this award and noted that the Board would be voting on it. It is hoped that this portable award will give extraordinary young researchers the opportunity and incentive to move into or stay in the cancer field and help them embark on an independent career.

Dr. Klausner referred to the two priorities he announced earlier in his presentation. One was to create and maintain the opportunity for discovery, and the other was to ensure that discoveries are translated for the benefit of patients. This translation requires a successful clinical research system. Dr. Klausner explained that, in addition to providing increased funding for clinical research, dealing with the changes of the health care system in relation to opportunities to participate in clinical trials will be important. There is concern that, as patients move into managed care organizations which look to cost as the bottom line, the ability to accrue individuals to participate in clinical trials may be lost. Dr. Klausner acknowledged Dr. Robert Wittes and Ms. Mary McCabe for their efforts in creating opportunities and models for dealing with the relationship between the current provider-payer environment and the clinical research enterprise.

Dr. Klausner announced that, on March 4, he will be signing an agreement with the Department of Defense (DoD) to provide a model for providers and payers to understand their responsibility in ensuring that the clinical research and clinical trials systems remain healthy. The NCI-DoD agreement is a 3-year demonstration project to enable and enhance access to the NCI clinical trials system to all participants of the 8.3M member provider-payer system of the DoD. The DoD agrees to pay the clinical costs associated with being evaluated for eligibility and participating in NCI-sponsored Phase II and Phase III trials. Dr. Klausner explained that there are four definitions for NCI sponsorship: Cancer Therapy Evaluation Program (CTEP)-approved trials; trials going through the Cooperative Groups system; trials supported directly by NCI funds; and trials established, conducted, and monitored at the NCI Cancer Centers. Dr. Klausner indicated that patients from the DoD system are already being accrued into trials. The NCI is committed to providing the information gained from this demonstration project (concerning outcomes and the true cost of connecting a large payer-provider system to the NCI trial system) to the DoD participants and providers.

Dr. Klausner moved the discussion to the draft of the new bypass budget. The bypass budget, which is about 65 pages long and user friendly, explains what the NCI is and what it does, and describes new opportunities and investments. Dr. Klausner added that the bypass budget discusses the opportunity to transform clinical oncology fundamentally through cancer biology. Dr. Klausner asked the Board to comment on the bypass budget by March 4.

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# REPORT OF THE DIRECTOR NATIONAL CANCER INSTITUTE QUESTIONS AND ANSWERS

Dr. Rimer thanked Dr. Klausner for his presentation and welcomed any comments or questions from the Board. Dr. Philip Schein commented that the change in the paylines for clinical research and the expedited reviews are welcome additions that respond to the Board's concerns about the gradual demise of clinical research. Dr. Schein explained that because there is a delay between receipt of the returned grant and the need to respond to the various critiques, institutional directors of these programs will have to support the individual during that bridge period and must be aware that this mechanism to work in cooperation with the NCI is available. Dr. Schein asked Dr. Klausner what programs he is going to put in place to inform program directors that this mechanism is operational. Dr. Klausner responded that the NCI is advertising heavily by covering the issue in different journals, sending letters, speaking to professional societies, and putting information on the NCI HomePage. The NCI wants grantees to recognize this opportunity and use it. Dr. Klausner indicated that the NCI is open to any other ideas for communicating these changes.

Dr. Sydney Salmon asked whether the letter that goes to the applicant could provide information on the funding process and the rights of the applicant. Dr. Kalt answered that each eligible applicant is identified by program staff and receives a separate letter with the summary statement at the time the summary statement is mailed. Dr. Rimer commented that there will be mentoring so that applicants are given that message directly.

Dr. Boxer brought forth his concern that there has been a reduction in minorities receiving funding and noted that minority faculty decreased from three to one, a 66 percent drop. Dr. Kalt explained that the decrease reflects the fact that the NCI has not received investigator-initiated applications in that area.

Dr. Rimer thanked Dr. Klausner and introduced Ms. Dorothy Tisevich, the Legislative Liaison for the NCI, to give an update on current legislation.

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## LEGISLATIVE UPDATE

Ms. Tisevich noted that she would be presenting a brief legislative update, which she supplemented with a more detailed handout.

Ms. Tisevich announced that the Senate Labor and Human Resources Committee, which is chaired by Senator Nancy Kassebaum, will begin its hearings on the NIH Revitalization on March 6 and 7. Dr. Harold Varmus, Director of the NIH, Dr. Klausner, and several other Institute directors will testify on panels looking at various diseases and areas of research. She stated that the House Appropriations Committee hearings for the NIH will begin late in March, will be interrupted by a 2-week spring recess, and then will begin again in mid-April. The dates and times are still tentative. Public witness testimony is beginning this week before the House Appropriations Subcommittee and will continue next week.

Ms. Tisevich indicated that there have been several requests from Capitol Hill for briefings on various NCI activities, including those related to prostate cancer, cancer information dissemination, the International Cancer Information Center, and boron neutron capture therapy.

Ms. Tisevich pointed out the list of congressional departures in the legislative update handout, noting that several key members of the authorizing, appropriations, and oversight committees are leaving, including Senator Kassebaum and Senator Mark Hatfield.

Ms. Tisevich commented that the furloughs are over and that the NCI is funded through September 30, 1996.

The bill that was the vehicle for the funding action was the Commonwealth of Massachusetts's National Marine and Fishery Service Laboratory bill. She explained that the NIH was one of several programs that was singled out for funding, but there are still several agencies that face the possibility of furloughs on March 15, 1996, when the current continuing resolution expires.

Ms. Tisevich explained that, although no reauthorization (revitalization) bill has been enacted, it does not have an impact on the ability of the NIH to continue to function under the provisions of the PHS Act. She pointed out to the Board that from 1991 through 1993, the NCI was technically unauthorized but continued to function, and this may happen again if the reauthorization bill does not get enacted. Ms. Tisevich explained that the bill may not be enacted because there are many controversial provisions that may be added onto any bill that gets introduced by the Senate or the House.

Ms. Tisevich stated that there is information in the handout about some FDA reauthorization bills that have been introduced. Ms. Tisevich then discussed several hearings. Senator Kassebaum held hearings last week on FDA reauthorization and Representative Bill Aracus is holding hearings this week. Dr. David Kessler has testified. Dr. Bruce Chabner, the former Director of the Division of Cancer Treatment (DCT), testified before Senator Kassebaum last weekend and is scheduled to testify before Representative Aracus this week. Ms. Tisevich reported that one of the more controversial provisions about FDA reauthorization has been off-label use of drugs. FDA's position is that there should be some restrictions on the ability of drug companies to distribute literature about off-label indications. Ms. Tisevich informed the Board that she has copies of some of the testimony available for anyone who is interested.

Ms. Tisevich continued that there are four bills on the protection against genetic discrimination. Some of these bills prohibit providers from denying or canceling health insurance coverage or making changes to premiums or terms and conditions for coverage on the basis of genetic information, or even on the basis that an individual family member has requested genetic services. Some of the bills also protect the ability of researchers to use genetic information for research through confidentiality measures.

Ms. Tisevich explained that five bills currently introduced are dealing with biomedical research trust funds. These bills provide a vehicle for setting up a trust fund specifically for biomedical research through either additional taxes on tobacco products or check-offs on income tax returns. She noted that more information about these bills are provided in the legislative update.

Ms. Tisevich announced that Senators Hatfield and Kennedy introduced the Clinical Research Enhancement Act, which is directed towards the NIH and provides additional support for and directives to expand clinical research programs. This Act establishes a President's Clinical Research Advisory Panel through the Office of Science and Technology Policy. It requires an evaluation of the status of clinical research and the submission of periodic progress reports to the President. It is possible that some of these provisions might be included in an NIH reauthorization bill that may be introduced.

Ms. Tisevich noted that there was a question at the last NCAB meeting about antiemetics. She explained that there was an amendment offered that would deny coverage through Medicare of all uses of antiemetics. The vehicle for this was the Budget Reconciliation bill, which was vetoed. She informed the Board that those provisions have not gone anywhere and that, under current Medicare reimbursement procedures, it is possible that another version of Budget Reconciliation will again be introduced.

Ms. Tisevich welcomed questions from the Board.

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## LEGISLATIVE UPDATE QUESTION AND ANSWER

Dr. Rimer thanked Ms. Tisevich for her succinct summary of many legislative activities and asked if there were

any questions or comments. Ms. Deborah Mayer asked for an update on the latest summation information. Ms. Tisevich noted that there is a summary in the legislative update handout and mentioned that there have not been any hearings since the meeting.

Ms. Frances Visco asked for clarification on whether there are two genetic discrimination bills on the Hill. Ms. Tisevich confirmed that there are two, one by Congresswoman Louise Slaughter and the other by Congressman Clifford Stearns and Senator Hatfield.

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## **NEW BUSINESS SESSION I**

Dr. Rimer opened the floor for identification of new business to be discussed during the second new business session on the following day. Dr. Dickersin announced that, in her subcommittee meeting the previous evening, it was suggested that the NCAB discuss restructuring its subcommittees. Dr. Rimer agreed that it is time to think about reinventing some of the subcommittees, noting that the NCAB is in the process of scheduling a Board retreat in June. It is hoped that by June, there will be new members with whom the structuring can be discussed.

### **Delegation of Authority**

With no other new business, Dr. Rimer moved the discussion to delegation of authority. Dr. Kalt stated that under the special authorities of the Director of the NCI in the Public Health Service Act, there are a number of routine requests made of the Board to allow it to take administrative actions to facilitate the programs. He noted that there is a set of unique intramural training programs that the NCI runs; eight currently in existence are listed in the Board's agenda books.

There are also three administrative supplemental delegations of authority, which are listed as A, B, and C in the Board notebook. The first allows Dr. Klausner, as the Director of the NCI, to appoint 151 experts. This is a personnel classification in the Federal Government that allows people to be hired to work for the NCI for 1 to 5 years. The second provides the ability to appoint additional advisory committees or components of the private sector and State and local government officials to advise the Director with respect to his function. The third is used for each Board round to make administrative adjustments related to applications and to awards that are within defined budgetary limits.

Dr. Kalt explained that all of these delegations have been in effect and are being put on the table to allow the Board to comment and entertain a motion to continue them in the future. A motion to continue these delegations was made and unanimously approved. After asking for any further questions or comments, Dr. Rimer closed the session.

Dr. Rimer introduced Dr. John Glick, President of the American Society of Clinical Oncology, to discuss some of ASCO's activities.

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## **REMARKS FROM THE PRESIDENT, AMERICAN SOCIETY OF CLINICAL ONCOLOGY**

Dr. Glick explained that he would be discussing some of ASCO's initiatives and the cooperative relationship it has developed with the NCI and other organizations.

Dr. Glick began by outlining the ASCO membership profile. He showed a slide indicating that ASCO is an organization of more than 10,000 members. It is growing at a rate of 6 to 8 percent a year. Fifteen percent of its

membership is from abroad and Canada. Of the members who answered ASCO's survey, 35 percent are in academic medicine and 47 percent are in practice, including offices, hospitals, managed care organizations, and clinics. The majority of ASCO's members are in medical oncology and/or hematology, with 13 percent in radiation oncology, 6 percent in surgical oncology, 4 percent in pediatric oncology, and the remaining 3 percent in gynecologic oncology.

Next, Dr. Glick defined ASCO's mission and credo through a series of slides. ASCO's mission is "to improve the health and well-being of people with cancer," whether through research, education, or clinical care. ASCO's credo is to "do what's right for and in the best interest of people with cancer." This credo guides ASCO to decisions and priorities that are important for patients.

Dr. Glick then explained ASCO's goals. ASCO, a scientific and educational society, is responsible for the delivery of programs to and on behalf of its membership, and to the larger audience who attends its annual meetings. Dr. Glick noted that approximately 12,000 people attended last year's annual meeting. In the last 5 years, ASCO has expanded its goals and its programs. Dr. Glick presented more slides and explained that ASCO's advocacy programs are directed to educating outside groups about the needs of its membership and the needs of people with cancer. ASCO represents the needs of the academic oncology community across multidisciplinary and multispecialty lines. ASCO's initiatives are aimed primarily at advancing knowledge through clinical and patient-oriented research and the programs that accompany it. Also, ASCO is committed to basic research and increased funding for basic research, because this is where the generation of new ideas arise. But, Dr. Glick emphasized, its particular responsibility is in the area of clinical and patient-oriented research. ASCO's efforts are directed at improving the clinical practice of oncology. Dr. Glick stated that it is important for academic institutions and academic oncologists to recognize that the issues that affect practitioners in clinical oncology (reimbursement, coverage of patients in clinical trials, and off-label indications) also affect them. Similarly, the practice members of ASCO must have the tools of molecular biology and molecular genetics if they are going to practice oncology in the next generation. Greater than 80 percent of ASCO's members graduated from medical school more than 10 years ago, and some are not prepared to meet the challenges of modern biology. Thus, ASCO is dedicated to the training of future generations of cancer researchers and specialists.

Dr. Glick summarized ASCO's major priorities with several slides, noting that some of these priorities have been on its agenda for years, and others were reestablished and given its imprimatur at a strategic board retreat this past summer. First, it was decided that for ASCO's mission and credo to succeed, it was necessary to develop a partnership with the NCI and its leadership to achieve common goals. Dr. Glick commented that one of ASCO's greatest successes this year was the partnership it established with the NCI. The ASCO leadership and board met with Dr. Klausner within 2 weeks after he became Director of the NCI, and there was an immediate productive collegial dialogue. Dr. Klausner understood many of the needs of people with cancer, the needs for patient-oriented research, and the need for increased funding. Since this time, ASCO has accomplished more of its agenda than in many years previously.

Other key priorities are to increase funding for patient-oriented research and to improve training of clinical investigators. Dr. Glick cautioned that unless clinical investigators receive funding for their research and support for their training, they will be forced to see more patients to meet their salaries, and will be lost from research. Also, ASCO is placing an increasing emphasis on translational research in its scientific and education programs, while continuing its international and leadership role in the reporting of results from Phase II and Phase III clinical trials. At the ASCO meeting in May in Philadelphia, scientific and educational sessions will be integrated. Another ASCO priority is to expand its public policy activities on issues relevant to its mission and goals. Also, ASCO believes in promoting the reengineering of Phase III clinical trials, a goal discussed with the NCI.

Dr. Glick stated that for many years, ASCO has promoted insurance coverage for patients on approved clinical trials and for off-label uses of FDA-regulated products. He commented that ASCO clearly supports the NCI/DoD initiative. Other ASCO priorities include developing evidence-based clinical practice guidelines; establishing partnerships with patient advocacy organizations to achieve a common agenda; and developing

referral guidelines for patient access to cancer specialists. Dr. Glick stated that it is important that people with cancer have access to cancer specialists and other appropriately trained health care professionals, and that ASCO is working with the American Cancer Society and other professional oncologic societies to develop these referral guidelines. Also, in May, ASCO is launching ASCO OnLine for its membership through the World Wide Web.

Dr. Glick announced that ASCO has a definition of patient-oriented research. This definition, which Dr. Glick suggested may be remarkably similar to the definition proposed by the Nathan Committee, is as follows: "Clinical investigation in oncology is hypothesis-driven research that employs measurements in whole patients or normal human subjects, in conjunction with laboratory measurements as appropriate, on the subjects of clinical biology, natural history, prevention, screening, diagnosis, therapy, or epidemiology of neoplastic disease."

Dr. Glick stated that ASCO has argued for years for increased funding for patient-oriented research. Dr. Glick added that in its relationship with the NCI, ASCO sends its position papers to the NCI far in advance of their publication. Dr. Glick also mentioned the AER review of grants, and that ASCO will work to publicize this unique opportunity for patient-oriented researchers to be funded.

Dr. Glick then moved to a slide about improving the training of clinical investigators. Dr. Glick commented that ASCO was pleased to see an increased funding from the NCI in the budget this year for training grants, K08s, and other awards. He noted that ASCO has a grant program of young investigator and career development awards, which will approach approximately \$1.3M this year. Also, he announced that ASCO and the American Association for Cancer Research (AACR) are working together this summer to hold a 1-week clinical methods workshop for clinical investigators-in-training and junior faculty, with an outstanding group of speakers, workshops, and case studies. A training grant has been submitted to the NCI for support of this workshop. In addition, ASCO has a program of 100 merit awards for travel to the ASCO annual meeting for trainees whose papers are accepted to ASCO either as a poster or scientific session. Dr. Glick also noted that ASCO has a new associate membership category for young fellows in training from all disciplines.

Dr. Glick's next set of slides related to the development of evidence-based clinical practice guidelines, which are needed by patients, physicians, and the insurance industry. ASCO has made it a priority to prepare practice guidelines and technology assessments using evidence-based methodology to promote cost-effective, high-quality patient care. ASCO is using multidisciplinary expert panels with patient representatives, an increased budget, and full-time staff to develop up to four guidelines per year, as well as an expedited review by the ASCO board.

Dr. Glick then presented a slide listing the criteria for selection of topics for the evidence-based clinical practice guidelines. These criteria include the following: the disease or technology is common and the economic burden is high; the health condition is associated with high morbidity and/or high mortality; practice variations exist; and there is evidence available regarding the efficacy of relevant interventions.

The next slide showed the topics for the evidence-based clinical practice guidelines. The first topic included guidelines for the use of hematopoietic colony-stimulating factors (CSF), which were published in the *Journal of Clinical Oncology* in November 1994. Dr. Glick added that these guidelines have been widely accepted by Cancer Centers, the insurance industry, and other institutions. These guidelines are being updated on a yearly basis, and ASCO has just approved updating the CSF guidelines for use in acute myelogenous leukemia and for generation of progenitor peripheral blood stem cells.

Other guidelines, which will be published soon, are for the use of tumor markers in breast and colon cancer. Also to be provided are guidelines on the management of metastatic and locally unresectable nonsmall cell lung cancer; the economic burden for this type of lung cancer is high, and there is tremendous potential for practice variations. Also, ASCO has just formed panels for providing guidelines on the followup of patients with breast and colon cancer after local-regional treatment with or without adjuvant therapy. This panel will determine whether tests such as bone scans, blood work, and chest x-rays are needed, and whether they are cost effective. Dr. Glick continued that ASCO has just approved two guidelines, one for the management of metastatic

prostate cancer and the other for the use of antiemetic therapy.

Dr. Glick's next slide showed some of ASCO's public policy statements. Dr. Glick stated that ASCO has taken an increasingly proactive role this year in its public policy statements through its Public Issues Committee. He indicated to the Board that the ASCO's position paper for funding for patient-oriented research is included in their NCAB meeting book. The paper will soon be published in the Journal of Clinical Oncology. Another policy is medical oncology for the general medicine trainee. Because there is more emphasis on primary care, ASCO felt there was the need for guidelines in this area.

Dr. Glick noted that ASCO has completed a study on the medical oncology workforce and the current status and recommendations for the future, which has major implications for patient care and for clinical research. It appears that the appropriate number of medical oncologists are being trained to function in a managed care environment. Also, although before this year ASCO did not have a major public policy statement on tobacco control, its policy now clearly labels tobacco as an addictive substance and, along with the FDA and the NCI, ASCO is in favor of banning all tobacco advertising. ASCO has recently approved a statement, which will be published soon, on the physician and unorthodox cancer therapies. Finally, Dr. Glick stated that ASCO's statement on genetic testing for cancer susceptibility will be released to the general public. In developing this policy statement, ASCO involved patient representatives and representatives in the genome project; Dr. Glick noted that although this is an example of an area where ASCO disagrees with the NCI leadership, it is disagreeing in a collegial and productive manner.

Dr. Glick's last slide related to ASCO partnerships with patient advocacy organizations to achieve a common agenda. Working with these organizations is a priority of the ASCO's President and Executive Vice President, because it is the patients and their families who are most affected by cancer and cancer research. ASCO has already met with the Cancer Leadership Council, as well as some of the leaders of other patient advocacy organizations. Patient advocates are voting members of key ASCO committees, including the education and program committees, as well as of practice guideline expert panels and public policy subcommittees. ASCO membership for leaders of patient advocacy organization has been implemented and invitations have been sent. It is important that they become members of ASCO and that ASCO becomes members of their organizations. Various education programs at the annual meetings, which are of interest to the patient advocates and to ASCO physicians, include sessions on patient-physician communication, spirituality, and genetic issues related to genetic susceptibility testing. ASCO will have a patient advocacy kiosk and exhibit booth at its annual meeting.

In summary, Dr. Glick expressed that it has been an extraordinarily active 9 months since he became ASCO President, and the board of ASCO is strongly behind the initiatives discussed today. Dr. Glick emphasized that ASCO has established relationships with other professional societies, patient advocacy organizations, the NIH, and the NCI to achieve a common agenda.

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## **REMARKS FROM THE PRESIDENT AMERICAN SOCIETY OF CLINICAL ONCOLOGY QUESTIONS AND ANSWERS**

Dr. Rimer thanked Dr. Glick and asked for comments or questions from the Board.

Dr. Ellen Sigal complimented Dr. Glick and ASCO on its complicated and exciting agenda, and then asked how ASCO is working with managed care providers and insurance companies in developing guidelines for treatment. Dr. Glick answered that ASCO's expert panels are developing guidelines without representatives from managed care organizations or insurers to remain free of any conflict of interest, although these groups have encouraged ASCO and other professional societies to produce the guidelines. Dr. Glick indicated that the managed care organizations adopted its CSF guidelines, which may mean that they also will be supportive of ASCO's other evidence-based guidelines.



Dr. Schein voiced his concern that guidelines can become a set of restrictive regulatory documents. He recognized that for many diseases, state-of-the-art treatment is unsatisfactory; thus, it may be impossible to define a suitable set of guidelines for a specific disease state. Dr. Schein cautioned that guidelines must be prepared carefully so as not to be too restrictive, stifling investigators and discovery at a time when discovery is so important. Dr. Glick agreed with Dr. Schein, and explained that the charge to the guideline panels is to implement clinical patient-oriented research into the guidelines, ensure that a mechanism is in place for updating the guidelines every year based on the current research, and use the evidence-based methodology. For example, although many have urged ASCO to develop a guideline on the use of stem cell or marrow transplantation in breast cancer, the evidence is simply not there and ASCO has therefore chosen not to provide that guideline. Also, mechanisms are in place to do a full, large-scale evaluation of each guideline every 3 years.

Dr. Klausner added that his relationship with Dr. Glick, as well as the NCI's relationship with the ASCO leadership, is productive and enjoyable. They are discussing many of the initiatives to ensure that programs are implemented in a way that makes sense to academic medicine and to medical practice.

Dr. Salmon inquired whether there are any plans for ASCO to disseminate the guidelines to managed care organizations through means other than publication in a journal. He noted that in the medical curricula of many medical schools, there is not an organized, coordinated block in education and oncology. Because primary care practitioners are given increasing responsibility with cancer patients, often determining whether they should be referred for treatment, this is of increasing importance. Dr. Glick agreed that it is a terrific idea to send the guidelines to all the insurance companies and managed care organizations. Dr. Stacy Beckhart from ASCO added that ASCO is working with its legal counsel to implement that idea. As a major medical specialty society, there are some limitations about what ASCO can do with respect to "reinforcement" of the guidelines.

Dr. Dickersin asked Dr. Glick to describe briefly how ASCO identifies patient representatives. Her concern is that these representatives be associated with constituencies so that there can be an exchange of information. Dr. Glick explained that ASCO has approached some of the patient advocacy organizations and asked them to nominate representatives to serve on the expert guideline panels. He noted that there is a patient representative on ASCO OnLine.

Ms. Mayer asked what type of collaborations exist or will be planned for other groups that are developing guidelines, such as the National Comprehensive Cancer Network (NCCN). Dr. Glick indicated that ASCO does not have a liaison with NCCN, but when ASCO plans to develop a guideline, it speaks to those professional societies the guideline may affect and asks them if they wish to send a liaison member to the expert panel.

Dr. Rimer thanked Dr. Glick, adding that ASCO's statements on tobacco control and genetic susceptibility are going to be very important, and that the statement on genetic susceptibility in particular will generate a lot of healthy debate.

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## RECOGNITION OF OUTGOING MEMBERS

Dr. Rimer announced that outgoing members would now be acknowledged by the Board. Although time did not permit the acknowledgement of each individual's contributions, Dr. Rimer recognized the fact that each outgoing member made unique contributions, and that she has enjoyed working with all of them. Dr. Rimer then called each of them to the podium, beginning with Dr. Becker.

Dr. Becker noted that as a participant of the NCAB, he has been privileged to hear the revelation of many scholarly works, and he hoped that the NCAB would continue to eliminate fruitless processing by pursuing its actions, demanding responses, and determining whether its recommendations have been fulfilled. Dr. Becker emphasized the importance of proactively guiding policy in the use of valuable funds. Dr. Becker stated that he found the dedication of many members of the NCAB, as well as many members of the NCI staff, scientists, and clinicians, impressive.

Dr. Rimer then called on Dr. Kenneth Chan. Dr. Chan thanked Dr. Rimer, Dr. Klausner, and members of the Board for their kind recognition. He expressed his gratitude to all of his colleagues for their assistance and thoughtful discussion and exchange of ideas during the past 5 years. Dr. Chan expressed particular gratitude to the late Dr. Howard Temin, who was an excellent coach with regard to Board activities and devoted to cancer research. Dr. Chan added that the establishment of the Howard Temin Award is in high accord with this recognition. Dr. Chan expressed his hope that more scientists from other minority groups will serve on the Board in the future, and that he will not be the last one from Asiatic origin. Also, Dr. Chan reminded the Board that it was established by the National Cancer Act as part of the effort to wage the war on cancer. The nation and public entrusts the Board to use the tax dollars to help this country to eradicate cancer. He noted that much progress in understanding the cause of cancer has been made. Although many genes have been identified that relate to the cause of cancer, there is another factor— smoking—that kills over one-third of the half-million Americans who die from cancer every year. However, the country has failed to reduce the mortality caused by smoking. Difficult tasks ahead include working with the legislature to regulate sales of tobacco products and convincing young people to give up smoking.

Dr. Rimer thanked Dr. Chan and recognized Ms. Marlene Malek, noting that she has been particularly grateful for Ms. Malek's help in the area of cancer control. Dr. Rimer announced that Ms. Malek will continue to work with the Board on the summit on women and tobacco. Ms. Malek expressed that it has been an honor for her to work with such outstanding and dedicated individuals on the Board and the staff at the NCI. She assured the Board that she will continue to help wherever she can in the fight against cancer.

Dr. Rimer announced Ms. Mayer, acknowledging Ms. Mayer's concerns about mentoring new Board members. Ms. Mayer thanked the Board and assured them she would continue to help bring new members onto the Board.

Finally, Dr. Rimer acknowledged Dr. Salmon. Dr. Salmon stated that it has been a pleasure for him to serve on the Board, and that the service has had both high points and low points. Some of the low points were times when the advisory function of the Board was either ignored or not sought; high points were seeing the reorganization of the NCI under new leadership, and a new open approach wherein the advisory function of the Board will be given high emphasis. Dr. Salmon echoed the comments of the others that the NCI staff has been extremely supportive, working under sometimes difficult circumstances, especially this past year.

Dr. Klausner noted that he has appreciated the outgoing members' advice and will continue to seek it. On behalf of the NCI and the entire nation's efforts against cancer, Dr. Klausner acknowledged the enormous amount of work that the members had done. Dr. Rimer indicated that because there are no new appointments yet, the outgoing members may have to return for the May NCAB meeting. She hoped to let them know the status as soon as possible.

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## THE ROLE OF THE BIOTECHNOLOGY INDUSTRY IN THE NATIONAL CANCER PROGRAM

Dr. Rimer noted that the role of the biotechnology industry in the National Cancer Program is an area that was identified by the Board as extremely important and worthy of its attention. She explained that the presentations on this topic would help the Board evaluate both how it can collaborate with the biotechnology industry and where it needs only to be an informed observer of the industry. Dr. Rimer then turned the session over to Dr. Schein.

Dr. Schein thanked the invited speakers for taking the time to present to the NCAB. He noted that this is one of the few instances where the Board has devoted a significant portion of its agenda to a nonacademic subset of the private sector, specifically the emerging pharmaceutical/ biotechnology industry. This is, in part, a reflection of how far this industry has progressed during the past decade, as well as its current and future importance as a

resource to the National Cancer Program. Dr. Schein explained that there are well founded expectations that many of the future developments in cancer risk assessment, diagnosis, and therapy will find their origins and undergo development under the sponsorship of the biotechnology industry, perhaps in cooperation with academic centers of medicine and science, as well as with the NCI.

Dr. Schein commented that the process of taking a research concept and merging it into a deliverable diagnostic modality or treatment for the general public is a daunting exercise. In the process, the industry must commit the investment of vast budgets and many years of risk-laden development in an effort to achieve regulatory approval and commercialization. Although some of the early biotechnology companies have now matured to the point of integration and self-sufficiency, the majority will not reach the stage of profitability for quite some time.

Dr. Schein noted that in view of the almost explosive growth of the biotechnology industry and its anticipated importance for both the medical and economic health of the country, serious questions are being raised as to whether the current level of effort can be sustained. Small companies face the same challenges as their larger and more established counterparts, but without the resources that allow them to respond effectively to the delays and setbacks that are a part of the development process. As a consequence, there is concern that many of the newly created resources may soon be lost through either attrition or acquisition.

Dr. Schein stated that approximately 50 percent of small companies have inadequate cash reserves to allow them to survive beyond 2 years. Therefore, some of these small companies have had to change their mission from striving for full integration to serving as a seedbed of innovation, feeding their discoveries into the larger, more established pharmaceutical companies that have the required staying power. However, these arrangements required for survival have caused many small companies to become increasingly dependent on the priorities of their larger corporate partners and, perhaps, to lose their ability to innovate. In addition, although consolidation is a major theme, the headquarters of the acquirer is frequently based in Europe. One concern is that the resources to invent and produce a new drug whose development is supported by American taxpayers and investors is increasingly under the control of foreign corporations.

Dr. Schein announced that an outstanding group of experts in their respective fields have been invited to speak to the Board to provide insights on the many issues and challenges that face the biotechnology industry. Dr. Schein stated that he would briefly introduce each of the speakers before proceeding with the presentations.

Dr. Schein indicated that the first speaker would be Dr. Fred Craves, who earned his Ph.D. in pharmacology and experimental toxicology from the University of California in San Francisco. Dr. Craves founded several biotechnology companies, including Creative Biomolecules and Codon. He served as chairman and CEO of Codon at a time when it was acquired by the German pharmaceutical company, Schering AG. Berlex Biosciences was formed through the subsequent acquisition of Triton Biosciences. Dr. Schein explained that it was during this time that Berlex received FDA approval for fludarabine, a drug developed in cooperation with the NCI for therapy for chronic lymphocytic leukemia. In 1993, Dr. Craves left Schering AG and founded a private merchant banking firm, where he currently serves as chairman. Dr. Craves will address the contributions of the biotechnology industry to the National Cancer Program.

Dr. Schein announced the second speaker, Dr. Alan Goldhammer, the Director for Technical Affairs of the Biotechnology Industry Organization (BIO), who received his Ph.D. in biological chemistry from Indiana University. In his current position, Dr. Goldhammer serves as a direct liaison between the biotechnology industry and the FDA and has had several recent meetings with Dr. Kessler. Dr. Goldhammer will address the major issues under discussion in regard to FDA reform.

Dr. Schein noted that the third presenter would be Mr. Brian Poissant, a partner in the Pennie and Edmonds law firm, which is recognized for its expertise in pharmaceutical and biotechnology patent law. Dr. Schein commented that one of the areas of industry-academic interactions where there is considerable tension is the prevention of premature disclosure of proprietary information until after a patent has been submitted. A company is unlikely to provide the financial and other resources required to develop a product if the product

does not remain proprietary for a long enough period to allow a return on investment.

Dr. Schein informed Board members that the fourth presenter would be Mr. Dennis Purcell, managing director of Life Sciences Investment Banking with Hambrecht and Quist, a leading Wall Street banking firm that supports the biotechnology industry. Mr. Purcell also has served on the Board of Directors of many technology companies and, as such, comes with a unique perspective as to the financial needs of an emerging company, as well as the probability of maintaining financial support for the large number of companies that have proliferated over the past decade. Dr. Schein commented on the long timeframes required to bring a product from discovery to full development and FDA submission. Companies require sufficient capital to sustain themselves through this protracted period. Dr. Schein noted that the capital markets have become increasingly worried about the prospects of small companies in the biotechnology sector, in part because of several highly visible product failures.

Dr. Schein then explained that many of the scientific discoveries under commercial development originated in academically-based laboratories. Although in the past academic institutions were relatively naive to the potential value of their research programs, many now have developed active offices of business development to seek commercial partners for their products. Dr. Schein indicated that a unique set of relationships needs to be managed when the responsibility for the future development of the product is transferred to the commercial organization. Dr. Schein then announced that the next speaker, Dr. Mitchell Sayare, chairman and CEO of Immunogen, is responsible for the development of several anticancer therapies that originated in laboratories at the Farber Center. Dr. Schein explained that Dr. Sayare is in a unique position to describe to the Board the nature of the alliances that can be formed and some of the management challenges faced by a CEO of a small biotechnology company.

Dr. Schein noted that next, Dr. Wittes, well known to the Board, would describe the nature of the collaborations that have been established between the NCI and the biotechnology industry, followed by a presentation by Dr. Tom Mays, who is Director of the NCI's Office of Technology Development. Dr. Mays will discuss the current thinking of the NCI in regard to the future of such alliances.

Dr. Schein expressed his hope that these presentation would provide the Board and the NCI with a broader perspective of the potential for the biotechnology sector to contribute to the National Cancer Program, as well as the environment in which these new and sometimes fragile companies attempt to work and grow. Dr. Schein then asked Dr. Craves to make his presentation.

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## CONTRIBUTIONS OF THE BIOTECHNOLOGY INDUSTRY TO THE NATIONAL CANCER PROGRAM

Dr. Craves indicated that it is important to note the change in the definition of biotechnology. Biotechnology used to be defined as companies that work with molecular and cell biology, but today is defined as a diversity of technologies and practices that lead to innovation. All biotechnology companies today have common boundaries on startup and similarities related to the financing and development required to achieve sustainability.

Before presenting his first slide, Dr. Craves explained that he does not endorse any particular product or company through their inclusion on a slide. Dr. Craves then presented a slide showing what has happened in the formation of companies in the biotechnology industry in the last 25 years. He explained that the biotechnology industry began growing in the early 1970's. In 1993, there were fewer startups; then in 1994 and 1995, the industry picked up. Dr. Craves projected that there will be substantially more growth in 1996.

Dr. Craves noted that there are approximately 1,300 biotechnology companies, of which about 300 are public. Approximately 70 percent of the 1,300 companies are involved in health care, and the other 30 percent are involved in agricultural or environmental activities. Dr. Craves added that there are about 700 biotechnology

companies in Europe as well.

Dr. Craves explained that Mr. Steve Burrill and his colleagues at Ernst and Young conduct a survey of the biotechnology industry each year and develop the Merck/Biotechnology Index, which he showed on a slide. An aggregate of the biotechnology industry, which is a consolidation of numbers for all of the public biotechnology companies, is compared with Merck, a company that is a good benchmark for innovation in research and development (R&D). Dr. Craves noted that the numbers on the slide are approximately one year old. For the new year, Dr. Craves stated that the revenues, R&D expenses, market cap, and employees in the biotechnology industry will increase. Specifically, revenues are expected to reach \$13B in the ensuing year, and R&D expenses will be over \$8B. Net income to decrease the loss and the market cap is up substantially. Dr. Craves added that there are now approximately 115,000 employees in the biotechnology industry. These employees are predominantly from academic and government laboratories, rather than from the major pharmaceutical companies.

Dr. Craves showed a slide depicting the diverse mix of business models in the biotechnology companies. He noted that few companies in the biotechnology sector have become fully vertically integrated; Amgen is the most obvious of these. Most of the management in the industry has been very pragmatic and creative about establishing alliances.

Dr. Craves presented a breakdown of the biotechnology companies into diagnostic companies, therapeutic companies, and service companies. He showed a slide describing a few diagnostic products that are in registration today. These products are all in vivo imaging agents for prostate cancer, bowel cancer, and lung cancer. Dr. Craves' next slide presented other unique approaches to cancer diagnostics. For example, NeoProbe, a company that is integrating both diagnostics and therapeutics, has a novel way of detecting metastases and then using a cellular therapy approach to address the possible treatment of those metastases. Dr. Craves presented a slide listing companies involved in the development of new diagnostic technologies for cancer, and emphasized the large amount of activity in the broad-based diagnostic and device sector.

Dr. Craves then turned to therapeutics, grouping them into many categories, including antibiotics, alkylating compounds, antimetabolites, photodynamic therapies, radio/chemosensitizers, and chemoprotectants. Dr. Craves showed a slide listing companies that are involved in formulation technologies to improve the therapeutic index of drugs that are reasonably well known and characterized, as well as more novel compounds. Dr. Craves' next slide on therapeutics showed companies that have looked at new ways to formulate drugs to deal with depositions in solid tumors, to decrease the toxicity of compounds, and to improve the local concentration at the site of the tumor. In another slide, Dr. Craves presented formulated drugs that have been characterized and determined to be very toxic without having this kind of a formulation. He also listed a few companies that are working on the antimetabolites.

Dr. Craves presented a slide listing companies involved in the management of adverse treatment sequelae, an area where there is a large amount of activity. Dr. Craves noted that this is the kind of work a major pharmaceutical company could have done but did not do. Dr. Craves explained that pilocarpine has been used medically since the 1890's. MGI Pharma had the courage to develop a new formulation and obtained approval of it for xerostomia resulting from radiation treatment for head and neck cancer.

Presenting several more slides, Dr. Craves showed examples of companies working on radio/chemosensitizers, radio/chemoprotectants, and photodynamic therapy. Dr. Craves emphasized that QLT PhotoTherapeutics, a Vancouver-based company, has the first approved product for photodynamic therapy. This company had to go through a complex process of getting approval for lasers as well as for the drug itself, and they are now expanding the label clearance for the use of this compound.

Dr. Craves noted that a number of small companies have identified product opportunities for the markets he described. These product opportunities, in which the major pharmaceutical companies do not invest research dollars, are probably in the \$25M to \$75M range. Dr. Craves explained that the biotechnology companies in this sector of the business provide a major service by using these reformulation technologies to improve

therapeutic index.

Dr. Craves moved the discussion to biologics and showed a slide. He noted that, in terms of product sales, the most successful product that has been developed by the biotechnology sector is Neupogen, which was developed by Amgen. Amgen was established in 1982 and is now a Fortune 50 company. Dr. Craves reviewed slides listing the names of several other companies, including Chiron, Genentech, Viagen, IDEC, and Centocor, that are working with biological approaches to treating cancer. Dr. Craves added that therapeutic vaccines are still at an early stage of development, as are genetic therapies. He showed several slides listing some of the companies involved in this work.

Dr. Craves announced that he would briefly mention service companies. He showed a slide of one service company, Response Oncology, noting that there are several other companies or divisions of other companies that have been formed recently to deal with management of a particular kind of cancer. Dr. Craves stated that what is significant about these companies is that they form a system to synthesize and integrate the latest clinical practice and management of particular cancers. Dr. Craves predicted that there will be more cooperation between service companies, biotechnology companies who are developing the innovations, and health care providers.

Dr. Craves presented a series of slides illustrating the contributions that the biotechnology industry has made to approved products for cancer. He noted that although the industry is young, real products have been developed. Dr. Craves indicated that 20 to 25 percent of the products that are being sold by the biotechnology industry are directed towards cancer. He showed a few slides listing oncology products that are in Phase III clinical trials.

Dr. Craves presented more slides and suggested that a true evolution in drug discovery, based on new drug discovery tools, is being experienced. Drug discovery tools include genomics, combinatorial chemistry, high throughput screening, and information technology. Although these tools will be applied broadly, there will continue to be a disproportionate emphasis on cancer, the focus of most of these companies. Given the new tools available through genomics, Dr. Craves expressed that there is now an unprecedented opportunity to understand the molecular basis of cancer. The ability to diagnose, treat, and determine the appropriate treatment through prognosis is beginning to change dramatically. Dr. Craves also mentioned that the new combinatorial chemistries producing new molecular diversities will allow us to see the power of these technologies.

Dr. Craves' next set of slides explained that the high throughput screening process is being pioneered by many small companies that use process automation to screen very large numbers of compounds. Next, Dr. Craves showed a slide on information technology, which has become a central issue. The drug development process is an iterative one and, at various stages in the process, partnerships with major pharmaceutical companies can be made. Dr. Craves indicated that the amount of time and resources needed for the drug development process has been reduced, changing the way the industry thinks and plans. Companies budget their programs in terms of how many thousands of days between the time a target is identified and the time it enters the clinic.

Dr. Craves concluded that, collectively, the government, academia, and the private sector create a new national resource for providing the tools to develop a better solution to the problem of cancer.

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## **REGULATORY POLICY AND REFORM AS IT AFFECTS THE BIOTECHNOLOGY INDUSTRY**

Dr. Goldhammer explained that there is no question that the biotechnology industry has had a profound effect on the treatment of cancer over the past two decades. The ability to clone and produce human proteins, as well as prepare large amounts of monoclonal antibodies, is opening up new avenues for therapy. Advances of the genome project and improved diagnostics are just touching on where the country may be in another 10 years.

Clearly, the ability to diagnose cancer and treat it at an earlier stage holds the promise for better patient outcome.

Dr. Goldhammer explained that the techniques of biotechnology initially pioneered by the small venture capital-funded companies have now been embraced by the larger pharmaceutical industry. However, the marked difference in size and resources between a multinational pharmaceutical company and a start-up biotechnology company has profound implications for drug development. A biotechnology company measures its resources in terms of months rather than years. If a drug development project fails, the company may fail with it. Therefore, the time that a new therapeutic spends in the clinical development process is critical. The average time to move a product from bench to bedside in the 1970's was 5 to 7 years. Today, that average time has extended to 10 to 12 years.

The cost of drug development also has increased dramatically, from \$70M in the 1970's to over \$359M in the mid-1980's. Some experts are projecting that this cost is going to approach \$1B by the turn of the century. During the past decade, the total cost to develop a new drug has increased by more than 8 percent per year above the general rate of inflation. The delay in approvals in the United States denies patients rapid access to needed therapies and increased cost of development drives up the price of end products.

Dr. Goldhammer explained that the focus of his presentation is twofold: How can interactions between the drug sponsors and the FDA be improved to optimize the clinical development process? And how can the dissemination of information to physicians be improved so that secondary uses of drugs can be delivered to the patients more quickly?

Dr. Goldhammer's first slide showed the timeline for the three phases of biotechnology drug development and how costs can escalate through these three phases. Dr. Goldhammer indicated that some of the data about the time spent in the three distinct phases of drug development were obtained from a study published in spring 1994 by researchers from Tufts University. Dr. Goldhammer added that a new study, which will be published shortly, demonstrated that the periods for preclinical and clinical drug development have stayed relatively constant, although the FDA review period has decreased. Dr. Goldhammer emphasized that the critical issue is how cost escalates through the clinical development process. The time that is spent in preclinical development, as well as the cost that the biotechnology company incurs, is minimal. The cost begins to escalate as the product enters the clinic. Efficacy trials require the enrollment of a large number of patients. As the biotechnology company begins to consider submitting an application to the FDA, it must consider construction of a manufacturing facility, which significantly adds to the cost. Once the Product License Application (PLA) is submitted to the FDA, the costs level off, because at this point the clinical trials and the manufacturing plant are completed.

Dr. Goldhammer then highlighted the fact that the review times at the FDA have been decreasing since the passage of the Prescription Drug User Fee Act in 1992. Both PhRMA, the trade association representing the pharmaceutical companies, and BIO worked with the FDA to draft review goals and establish a meaningful fee structure in which industry would provide \$360M over 5 years to the FDA to augment its review capabilities. In return for these user fees, the FDA agreed to work towards review and action on new priority drugs, including all new cancer drugs, in 6 months. An action does not necessarily connote an approval; it could be a nonapprovable letter or a request for further studies. FDA has been given sufficient resources to meet these goals and, in the most recent report to Congress, the FDA Commissioner noted that the agreed-upon timelines are being met ahead of schedule. Thus, the end portion of the three-stage process is already being addressed.

Dr. Goldhammer explained that the cost and complexity of clinical trials—that is, work necessary to gather data prior to the submission of an approval application—has increased significantly. The costs of tests and related procedures per patient between 1989 and 1993 increased by 69 percent, 118 percent, and 51 percent for Phase I, Phase II, and Phase III clinical trials, respectively. This contributed significantly to the lengthening of the drug development process. It is this area that BIO chose to focus on in its initial approach to FDA reform. Last February, following 2 months of intensive consultation with its member companies, BIO issued a White Paper on principles for FDA reform. Dr. Goldhammer showed a slide listing identified areas of "excessive FDA

regulation." Dr. Goldhammer noted that he would briefly review these areas and then discuss how each area may be addressed.

Dr. Goldhammer explained that the first problematic area is excessive regulation at the early stage clinical trial process, including the submission of Investigational New Drugs (INDs). Currently, over 60 percent of all Phase I INDs are filed by individual scientists at academic health centers. These investigations rarely lead to commercial therapies, and their consideration delays approval activities by FDA reviewers. The second area is needless submission of advertising and promotional materials prior to FDA approval. The third area is restrictions on the export of unapproved products to countries that have approved them and review of foreign labels for approved products being exported. The fourth is the requirement of prior FDA approval for minor manufacturing changes of well-characterized biotechnology products, even though prior approval is not required for traditional drugs, which is inconsistent regulatory policy. Another inconsistent regulatory policy is the requirement for both an Establishment License Application (ELA), which regulates the manufacturing process, and a PLA, which regulates and covers the efficacy for biotechnology products; this stands in marked contrast to the way that traditional drugs are regulated. Finally, the current regulations on lot release needlessly consume FDA resources, increase costs, and, in some cases, may delay patient access to biotechnology products. Some of these problems are based on antiquated regulations stemming from the Biologic Control Law, first passed in 1902.

Dr. Goldhammer indicated that the White Paper was distributed to the key policy makers in both the Administration and in Congress. Draft legislative language that would reduce the impediments towards drug development was drafted, and the FDA was engaged in dialogue to attempt administrative reforms of some of the outdated practices. Quarterly meetings with Commissioner Kessler have continued since last June in an effort to further streamline the FDA regulations.

The FDA announced two sets of key reforms—one last April and one last November. The FDA announced that well-characterized biotechnology therapeutics would be regulated in the same manner as conventional drugs. The ELA would no longer be required for these products. In addition, the requirement for manufacturers to submit a sample of each batch to FDA for certification was removed for this class of products. The FDA also announced an interim definition that covers only the therapeutic products of recombinant DNA or monoclonal antibody technology. The agency held a workshop in December to seek top scientific input towards refining and expanding this definition. Administrative rulemaking should be completed during the first half of this year to finalize this regulatory approach. Dr. Goldhammer expressed the hope that some of the diagnostics, as well as the vaccines that fit the definition of well-characterized, also would qualify for this path of regulatory release.

In addition, Dr. Goldhammer explained that changes in the manufacturing process for well-characterized biotechnology products would be streamlined. Manufacturers would no longer have to seek prior approval for most changes in the manner that is now required. This contrasts with the way that a drug manufacturer can implement a manufacturing change by simple implementation and notification to the FDA. Prior approval is not required.

Also, in November, FDA simplified the data package needed to begin a Phase I trial. Summaries of the preclinical data, rather than the entire package, would now be required. The FDA did this in response to the majority of industry-sponsored Phase I clinical trials moving to Europe, where clinical trials can begin with simple notification to the European regulatory bodies, instead of the more stringent type of data filings that are required by the FDA.

Legislation was introduced earlier this year to deal with the drug export issue. Dr. Goldhammer noted that drug exports are regulated as a result of a drafting error in the 1938 Food and Drug Cosmetic Act, banning the export of unapproved drugs. This was partially remedied several years ago with legislation permitting export to 21 listed countries, primarily those in Western Europe, Australia, Japan, New Zealand, and Canada. Today, the United States is the only country in the world that controls the shipment of unapproved drugs abroad. Dr. Goldhammer expressed that this is not a desirable policy and consumes FDA resources.



Broader FDA reform legislation was recently introduced by Senator Kassebaum. Several key principles advocated by BIO are in this bill, including the following three key provisions: relaxing FDA controls on the dissemination of peer-reviewed information; streamlining the approval of supplemental indications; and providing a framework for a collaborative approach to drug development. Companion legislation in the House is expected shortly. Dr. Goldhammer explained that there is a hearing today in the House Commerce Committee, and it is expected that legislation will be introduced concomitant with that hearing.

Dr. Goldhammer stated that each of the provisions has implications on both the development of new oncology drugs and the expansion of use of already approved drugs. The FDA has limited the dissemination of information from respected medical journals, textbooks, and the proceedings of major medical and scientific societies. These limitations sometimes deprive the medical community of easier access to important medical information, hurt patients, and do not advance public health.

Under current FDA guidelines, companies are prohibited from providing reprints of peer-reviewed articles unless the articles comport in every way with the approved product labeling. For instance, they may describe different doses than those approved by FDA; they may not contain as detailed a discussion of side effects; or they may describe a treatment of a different indication. Nevertheless, Dr. Goldhammer stated, physicians rely on peer-reviewed articles and other reputable scientific publications as an important source of information about medical advances. This is particularly acute in the oncology area, where many products are used outside of the FDA-approved indications. Dr. Goldhammer indicated that the FDA must recognize that the cost of conducting clinical trials for every cancer indication is prohibitive. Companies should be permitted to disseminate reprints of peer-reviewed articles and proceedings of scientific meetings to physicians regardless of whether those publications contain information about unapproved drugs or unapproved uses of approved drugs. The Kassebaum legislation addresses this matter.

Dr. Goldhammer noted that one major problem with the development of oncology drugs is that each new indication requires a separate clinical trial. It is often not clear how wide a range a drug will have. In the majority of cases, the drug sponsor pursues either the broadest indication or the one that is the most promising for that product, with the hope of adding follow-on indications afterwards. An example in the biotechnology industry has been alpha interferon, whose first indication was for hairy cell leukemia, which has a relatively small patient base. Since the time of first approval in 1983, six additional indications for both oncology and nononcology have been added to the label. Once the drug is approved by FDA, the physician can prescribe it for an off-label use. It is estimated that over half the current uses of anticancer drugs are for cancers other than those on the label. Supplementary indications are often slow to develop, because the original sponsor may not want to pursue a new trial, and the FDA may not give priority to follow-on indications.

In Senator Kassebaum's proposed legislation, there is a provision that would add new indications to the label, based on medical practice. If a drug is used for follow-on indications and the medical community recognizes this use as the standard of care, an additional indication can be added to the label following a petition to the FDA. There are some details to be worked out with respect to this provision, such as the length of time the product is in medical practice and the amount of data needed to demonstrate that the drug represents a new standard of care. However, it does address a real need for both patients and their physicians.

Dr. Goldhammer indicated that another area of focus is the improvement of the IND process. By streamlining certain activities, FDA can free up more review staff for interaction with sponsors during drug development. FDA should commit to a meeting with sponsors, in which clinical protocols are to be discussed, within 30 days of a request. Secondly, advice to sponsors should be made a part of the administrative record so that there is a firm understanding of the type of data required to support product approval. When a clinical trial is put "on hold," FDA should be obligated to inform the sponsor about what information is needed to get it "off hold." FDA has made a commitment to promptly review the data submitted to get a trial off hold, but if the sponsor does not know what the FDA's fundamental reasons for the hold are, it is difficult to address them. Dr. Goldhammer explained that BIO believes that there should be a firm timeframe for responses to the sponsor.

BIO also recommended initial steps to improving patient access to new therapies as part of transforming and

renewing the FDA. Promotion of the public health, increased international competitiveness, and prompt revision of regulations are paramount goals for renewing the FDA. A renewed FDA can serve the needs of the patient community, general public, and stakeholders by focusing its mission on promoting the timely approval of safe new drugs, biologics, and devices.

Dr. Goldhammer then speculated on whether legislative reform will occur this year. He noted that discussions with the FDA to achieve a meaningful administrative reform are ongoing, and it is hoped that enacting some of the provisions mentioned in his presentation today will help streamline the process.

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## INTELLECTUAL PROPERTY ISSUES

Mr. Poissant noted that the changes in the available modalities for the treatment of cancer have been phenomenal since he and Dr. Schein first met 10 years ago. He announced that he would discuss the issues facing a young biotechnology company in obtaining patents on their various discoveries, particularly in the context of three favorable changes that have taken place in the patent laws this past year. Mr. Poissant noted that he would also interrelate the patent issues to issues that face young biotechnology companies in raising money in the capital markets. It is becoming very important for companies to be advised and structured to be able to raise the money that they need to remain in business.

Mr. Poissant added that Dr. Schein sent him a provocative article by Dr. Steven Rosenberg of the NCI concerning the issue of secrecy in research, which appeared recently in the *New England Journal of Medicine*. One of the issues Dr. Rosenberg discussed was whether the patent system was detrimental to the overall good of cancer research because of the various secrecy requirements. Mr. Poissant explained that he would address this issue by interweaving it with the other issues he would be discussing today.

Mr. Poissant presented his first slide, which depicted a young biotechnology company and the various subject matters that they can seek to patent. These subject matters include genes, proteins, and processes. Mr. Poissant used the example of a young company that discovered a protein. The company would likely use screening techniques such as cDNA libraries and genomic DNA libraries, from which they discover the gene and the cDNA. The company would then put their discovery into a vector, then into a host cell, and then they would focus on the methods for making their recombinant products. Finally, the company would become involved in the various methods for using their new discoveries, such as diagnostics, drug screening, and therapy; gene therapy is the most prevalent. When the company presents its evidence to a patent lawyer, a decision must be made about what to patent. Although attempts sometimes are made to patent everything, often patents are obtained on the new proteins that have never been discovered before. Most frequently, patents are obtained on the genes and the vectors, as well as the recombinant methods used to produce them.

Mr. Poissant then drew attention to the three recent changes in the patent law and how they would affect the patent issues related to the example of a new company. First, Mr. Poissant stated, there was a clarification of the utility/enablement requirements. Starting around 1990, the patent office examiners began imposing a relatively high level of utility/enablement requirements. This meant that in a patent application, a large amount of data was required to demonstrate exactly what the product was supposed to do and that it, in fact, does what it is claimed to do. The level imposed was very difficult, almost requiring clinical data to show that the product was safe and efficacious. In the summer of 1995, the level of utility/enablement requirements was lowered significantly.

The second change was the recently passed biotechnology process patent legislation. This change occurred in response to a problem wherein the patent office would give a patent on a protein or on the gene that codes for the protein, but was reluctant to give patents on the recombinant production of the protein. The position of the patent office was that the recombinant production is known, and the fact that the protein is new or the gene itself is new does not entitle a biotechnology company to a patent on the process for making it. The new biotechnology process patent legislation states that if the product is new or if the starting material, namely the gene, is new, then presumptively the process for going from one to the other is also new. Thus, the patent office

now will be issuing patents on the recombinant process. This legislation also covered gene therapy.

Finally, Mr. Poissant discussed the three recent General Agreement for Tariff and Trade (GATT) changes in the patent law. The first and most notorious is that the term of a patent, which used to be 17 years from the date of issue, is now going to be 20 years from the date of filing. This change gives rise to many considerations about when a company should file. The second major change is that the patent office now accepts provisional applications, which means that a company can file a patent application and get a priority date, but its 20-year clock does not start ticking until approximately a year later when a "real" application is filed. The third change relates to interference contests, which are mini-litigations in the patent office that determine who was the first to file or who is truly the first inventor. Before this change, foreign inventors were limited to their foreign priority date. For example, even though the inventor who filed in Japan did work in Japan before that date, in a priority contest, the Japanese inventor could not rely on that work to beat an American inventor. This change will be monumental when it comes to advising clients, particularly companies going public whose underwriters want to know exactly what is going to happen and who is going to win if there is a priority contest.

Mr. Poissant's next slide showed the patent law visualized as being a three-legged stool. The seat of the stool is the patentable subject matter. The three legs of the stool represent the three things required to obtain a patent. The first leg is the utility and enablement requirement, which means enough evidence must be presented to the patent office to convince them a subject matter does what is claimed and works for its intended purpose. The second leg is novelty, which requires that no one else has done it before by way of publication or public use. The third leg is nonobviousness, which means what has been done is sufficiently different from what has been done before.

Next, Mr. Poissant discussed each of the legs of the stool separately and tied them into both the recent changes in the patent law and certain issues relating to the ability to obtain public financing, as well as Dr. Rosenberg's secrecy issues.

Mr. Poissant began with a slide about the utility and enablement requirement. As he mentioned earlier, around 1990 the patent office started imposing a very strict utility requirement and began virtually to require human clinical data, particularly for the cancer utilities. This was a serious hurdle and caused delays to obtaining patents. Applicants often filed credible *in vitro* and animal data, but the patent office would reject them, claiming utility and enablement was not proven. The applicant had to keep refiled the application until human clinical data was eventually obtained, which was often 4 to 6 years later. The other alternative was not to file until the clinical data was obtained, leaving open the possibility of someone else filing first. Last summer, the standard was significantly changed to whether asserted utility would be considered credible by a person of ordinary skill in the art, in view of all of the evidence of record. Most importantly, the patent office no longer requires human clinical data. *In vitro* or animal data is sufficient, if it is reasonably correlated to asserted utility in humans.

Mr. Poissant continued that the lowering of the utility requirement has many practical advantages. Applications can be filed earlier in the process and patents can be obtained more quickly. One of the problems raised by Dr. Rosenberg was that people were not disclosing their data publicly because they wanted to keep it secret until the patents were filed. The lowering of the requirement may alleviate the secrecy concerns espoused by Dr. Rosenberg, and dissemination of information may occur more effectively. This requirement change also is fortunate for the biotechnology industry in view of the new GATT 20-year rule. Because the patent term now runs 20 years from the date that it is filed, 5 or 6 years would have had to be spent fighting with the patent office over whether the utility and enablement requirement had been satisfied.

Mr. Poissant noted that the new GATT 20-year rule raises an interesting situation. Should a company file only to get a priority date and get credibility in the capital market, or should it wait to file until it has significantly sufficient data? Once a company files, the 20-year clock starts running, and it is better to delay filing until close to commercial reality so that the 20-year patent period is as commensurate as possible with the period of commercialization. However, this can be a dangerous approach because someone else may file first. When all these considerations are weighed, a young biotechnology company often must file, because it is difficult to have

credibility in a capital market without a patent application on file. One possible compromise could be the other GATT change, the provisional patent application, which allows the patent applicant to file but does not start the 20-year clock ticking. However, the company must file within a year to take advantage of that priority date. This provisional patent application is an important compromise that many young companies are now taking advantage of to get something on file for credibility, but not start the 20-year clock ticking immediately.

Mr. Poissant moved to his next slide, which related to novelty. He noted that Section 102 of the patent statute lists seven events, most involving publication or public use, that can take away a right to a patent. Research must be conducted to determine whether a claim has already been made. Although companies generally are already aware of what is going on and what has been published, patent lawyers search the Patent Cooperation Treaty (PCT) publications to find out what else is pending in the United States patent office. If someone files a patent in the United States, they have a year to file abroad, and they do this by filing in Washington with the PCT office. The advantage is that a company files in one place to get patent protection around the world; the disadvantage is that everyone can know, approximately 18 months after the fact, what is filed in the United States. Also, a company must be aware of the 18-month window, because although there may be no PCT publication out yet, there may be someone who is claiming the same discovery that they are. The company will not be aware of the claim until the patent office declares an interference. Then, a large amount of money must be spent in a priority contest in the patent office to determine who is truly the first inventor.

In these priority contests, the general rule as to who wins is the person that is the first to conceive the subject matter. Mr. Poissant referred back to his previous example, and posed the question: How does one conceive of a gene? A biotechnology company who has a protein and uses cDNA and genomic library screening to "fish out" the gene that codes for that protein has done a considerable amount of work. It is difficult, however, to determine when this company actually conceived of this gene. Once it is known that the protein exists, it is also known that the gene exists, although the specific gene may not be identified.

One of the first cases in Mr. Poissant's business—the Amgen versus Chugai case—resolved this issue by determining that one cannot conceive of a gene until the gene is both isolated and sequenced. This standard is known as "simultaneous conception and reduction to practice." Mr. Poissant referred back to Dr. Rosenberg's concerns about secrecy. The idea of simultaneous conception and reduction to practice, unlike the lowering of the utility standard, will have an adverse effect on the publishing of results. Now that the inventor is required to have the whole gene on file, they are not going to publish information about parts of the gene or various ways to look for it.

Next, Mr. Poissant addressed the effect of "expressed sequence tags," or ESTs, which are partial cDNA sequences that are synthesized from mRNA transcripts of unknown genes. Mr. Poissant commented that many companies are now getting these sequence tags and publishing them. In his judgement, publishing these ESTs will not have any effect on the ability to obtain the patents on the gene. Because ESTs are just partial sequences, they are not going to enable researchers to obtain the full gene.

Mr. Poissant showed his final slide to address two relatively straightforward issues on nonobviousness. The first related to obtaining patents on genes. Mr. Poissant explained that, for a while, the patent office would not give a patent on a gene just because the amino acid sequence or the peptide protein was known. This has been changed and overruled in "Re: Bell," which states that a patent on a gene can now be given unless the gene has been actually disclosed. Prior art must suggest the actual gene sequence and provide a reasonable expectation of successfully disclosing the gene. Mr. Poissant then discussed ESTs, which have no effect on the ability to get patents on the genes unless they are coupled with detailed information about how to use the EST to "fish out" the actual gene.

Finally, Mr. Poissant discussed the biotechnology process patent change that just took place. As he indicated earlier, the patent office had taken the position that even though the protein and the gene are patentable, the recombinant process of getting them is not patentable. Mr. Poissant explained that it may not seem important, because if you obtain a patent on the gene or the protein, others could still be prevented from making it recombinantly. However, as was seen in the Amgen versus Chugai case, this was important to foreign situations.

Amgen had a patent on the host cells and the DNA, but not on the recombinant process. Chugai was making the erythropoietin off shore and bringing it into the United States; however, Amgen could not do anything about this because they did not have a process patent. Therefore, Amgen could not take advantage of the Biotechnology Process Patent Act, which says products made by patented processes abroad cannot be imported. The Biotechnology Process Patent Act allows biotechnology companies to get patents on recombinant processes, which is important for preventing others from infringing and making the proteins and using their DNA and genes abroad. Mr. Poissant added that patent laws promote secrecy to some extent. However, the rewards resulting from patent laws promote research.

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## STATE OF THE CAPITAL MARKETS IN SUPPORT OF BIOTECHNOLOGY

Mr. Purcell informed the Board that 5 years ago this month he was diagnosed with chondrosarcoma and, as a former cancer patient, he was particularly gratified to speak at this meeting. Mr. Purcell explained that he was going to address the biotechnology industry from Wall Street's viewpoint, and provide an overview of how Wall Street sees the industry developing.

Mr. Purcell showed his first slide, noting that biotechnology is relatively new to Wall Street. In the 1980's, there were many questions about whether biotechnology would ever evolve into an industry. Since this time, the industry has come a long way. Mr. Purcell presented several slides showing that almost 9 out of 10 companies lost value in the stock market in 1994, then rebounded in 1995, when almost 8 out of 10 companies increased in value. Mr. Purcell commented that this volatility was risky for investors in the biotechnology sector. Consequently, many investors would not invest in the industry until they saw product approvals. Thus, companies such as Amgen, Genentech, and Biogen had flat stock prices until their products (Epogen, human growth hormone, and alpha interferon, respectively) were approved. Mr. Purcell informed the Board that of the 1,300 biotechnology companies in existence today, only 5 are profitable. Because many investors are interested in the later-stage companies, which include those 5 and perhaps another 25 or 30 companies, it is unknown what will happen to the remaining companies.

Mr. Purcell's next set of slides showed that many companies formed in the late 1980s will be coming to maturity over the next several years as they move products through clinical trials. The situation for some companies was bleak at this time last year because a number of negative trials put a damper on the industry. Mr. Purcell commented that the stock market punished those companies; the average loss after negative Phase III results was 51 percent. Likewise, almost half of all companies lost more than 50 percent of their value during the year. Signs indicating that the situation might improve began to appear. Mutual funds were abandoning the field, there were an increasing number of mergers, and there was increasing volume in the stock market in terms of numbers of shares that were traded. However, at this time last year, almost 50 percent of the companies had less than 2 years of cash left before they would go bankrupt.

Mr. Purcell noted that companies were relatively innovative, and presented a slide listing some biotechnology collaborations that were made with large pharmaceutical partners to try to stay alive. Interestingly, almost 70 percent of all biotechnology collaborations were with foreign pharmaceutical companies. Mr. Purcell's slides indicated that over the last 20 years, the NIH and other agencies have spent about \$40B developing the industry and, at this time last year, were on the verge of trading it away. Mr. Purcell informed the Board that the situation improved on June 12 of this year, when the initial Phase III result of Cephalon caused stocks to explode. With several other positive Phase II or Phase III results announced towards the end of 1995, the stock market became enchanted again with biotechnology, and stocks went up by almost 200 percent on average.

Mr. Purcell showed another slide and explained that when companies announce good clinical trial results, they are able to raise money in the capital markets. In the last 10 days, for example, Gilead Sciences raised \$150M, more money in an equity offering than any other biotechnology company existing today. Just 3 days ago, \$160M was raised for BioChemPharm, the Canadian company that has 3TC approval. Therefore, Mr. Purcell noted,

after either approvals or positive clinical trial results, Wall Street was willing to award those companies with relatively large amounts of money in terms of public offerings. However, it is still not known what will happen to the other 95 percent of the biotechnology universe.

Mr. Purcell explained that the biotechnology sector as it relates to Wall Street is influenced by a number of different factors. Market windows open up when there are a lot of product successes, when there is an optimistic environment, and when there is an absence of investment alternatives. Many investors are willing to take some risk in moving out of high technology, a hot sector of the economy for the last couple of years, and to look more at biotechnology companies. In fact, as the biotechnology companies stock prices went down, the risk/reward profile was more in synch with what investors were looking for. Mr. Purcell's slides showed that, consequently, the biotechnology industry had an astounding year. Biotechnology companies were up 80 percent, the leading industry segment as measured by Dow Jones in 1995.

Mr. Purcell's next slide demonstrated that, in 1995, \$2B was raised in the public markets for biotechnology companies, which is roughly equivalent to the NCI's budget this year. Mr. Purcell noted that the average of initial public offerings (IPO's) in the capital markets and "follow on's" (money raised for companies that are already trading) roughly equals this \$2B.

Mr. Purcell referred to the Merck-Biotechnology Comparison that Dr. Craves discussed in his presentation, noting that Merck has over a \$75B market cap, with the biotechnology industry overall well below that figure. If the top few companies that Mr. Purcell discussed earlier—Amgen, Genentech, and Biogen—are removed, the rest of the biotechnology universe would trade at the same value as a mid-sized drug company.

Mr. Purcell explained that although there is still a long way to go, 1995 was a more positive year for biotechnology companies than 1994. In 1995, both public offerings and corporate collaborations almost doubled that of 1994. Mr. Purcell showed a slide indicating that there are 140 different collaborations between biotechnology companies and corporate partners. Mr. Purcell indicated with another slide that the interaction with large pharmaceutical companies was one of the interesting interplays with the biotechnology industry last year. Pharmaceutical companies today hold over \$20B of cash on their balance sheets. Presenting more slides, Mr. Purcell noted that although they have a large number of drugs in the R&D pipeline, the bigger pharmaceutical companies are not convinced that they will have enough novel products and, therefore, are turning to biotechnology for these alliances.

Mr. Purcell commented on the difficulty that exists for a nonscientist or an investor on Wall Street to distinguish among all the alternatives in the biotechnology industry. There are 106 cancer products and 46 neurological products in the clinic. It will be a challenge for an average Wall Street investor to determine which of the 1,300 biotechnology companies may be one of the next profitable companies. Presenting more slides, Mr. Purcell noted that Wall Street has been disappointed in the slowness with which biotechnology companies responded to this difficult environment. Over the last year or two, the larger pharmaceutical companies have been more nimble than the smaller biotechnology companies. For example, in the space of 5 months, SmithKline Beecham completed four \$1B dollar transactions and completely reformed the company, while the biotechnology industry as a whole was facing severe liquidity problems. Mr. Purcell explained that the biotechnology industry has stayed constant in terms of the number of mergers or acquisitions that have occurred in order to compete in the new environment.

Mr. Purcell concluded with his thoughts on what Wall Street would like to see to help the climate become more positive for investment. First, the cost of discovery needs to be decreased. Mr. Purcell explained that "all or nothing" bets based on the results of Phase III studies are too risky for the average investor. Second, there needs to be a way to increase the gain on success, through either R&D credits or a change in the capital gains rate. Third, the patent system needs further improvements. Finally, changes in the product liability laws are needed that would give investors more protection for products after they are on the market.

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## COLLABORATIONS BETWEEN ACADEMIA

## AND THE BIOTECHNOLOGY INDUSTRY

Dr. Sayare presented his first slide and explained that he will describe the characteristics of relationships and collaborations between academia and industry. He noted that the company he works for, Immunogen, will serve as an example when discussing the challenges a company faces that are different from those of academia. He will state his opinion about the value that both academia and industry derive from these collaborations, the value derived by U.S. taxpayers, and finally the evolution of relationships between academia and the biotechnology industry over time.

Dr. Sayare's next slide covered biotechnology in the United States. He noted that nowhere else in the world is there a biotechnology industry as robust as the one in this country. In his opinion, this results from the convergence of three factors: entrepreneurship, venture capital, and availability of Federally-funded, cutting-edge research within the academic community.

Dr. Sayare commented that Americans are among the most entrepreneurial of people in the world, and that entrepreneurship is an essential element of building a biotechnology company. Also, the United States has more venture capital than anywhere else in the world. There are venture capitalists who put money into biotechnology companies and make money on those investments, leading to even more venture capital investments in biotechnology. The most important element is the availability of cutting-edge research that is publicly funded, meaning that all taxpayers are invested in the biotech industry.

Dr. Sayare explained that the origin and culture of biotechnology is what distinguishes it from the pharmaceutical industry. Most biotechnology companies originated with technology at a university. Because of that direct connection with the university setting, biotechnology companies live in that culture. Dr. Sayare feels it is that culture that has attracted good people to do the cutting-edge research in biotechnology.

Dr. Sayare presented a slide and discussed the collaboration that Immunogen has with Dana-Farber Cancer Institute in Boston. Immunogen, which is in Cambridge, was founded in 1981 with a \$3.5M investment on the part of two venture capital groups in Boston. The collaboration was based on a desire to use monoclonal antibodies to widen the therapeutic window of existing chemotherapeutics. Dana-Farber, then called Sydney Farber Cancer Institute, had just been taken over by Dr. Baruj Benacerraf. Dr. Benacerraf, Dr. Stuart Schlossman, and Dr. Lee Nadler put together a laboratory within the Dana-Farber Cancer Institute in which Immunogen's work was carried out. The research was funded for 5 years by Immunogen, whose first president was one of the venture capital investors. Twelve full-time staff were hired, six of whom had Ph.D's, to undertake this research at Dana-Farber, which involved connecting methotrexate and doxorubicin to monoclonal antibodies for delivery to cancer cells.

Dr. Sayare continued his discussion, explaining that Dr. Benacerraf insisted that the license agreement which underwrote the relationship between Immunogen and Dana-Farber be no longer than four pages. The relationship between Dana-Farber and Immunogen has been in existence for 15 years, and they now have a product that is in Phase III clinical studies. The technology platform that was developed at Dana-Farber by using the Immunogen money, however, was not doxorubicin or methotrexate attached to monoclonal antibodies, because these drugs are not toxic enough. Dr. Sayare explained that if a product can be delivered specifically to a tumor cell and nowhere else in the body, that product should be very toxic. Therefore, they developed a proprietary derivative of ricin, a potent plant toxin, that binds to and kills only the target cell to which the antibody is directed. The first such product, Oncolysin B, was developed for Non-Hodgkin's Lymphoma.

Immunogen also turned to the NCI, which provided a list of agents that had been screened and studied in the clinic. Immunogen developed the chemistries need to attach several of these agents to monoclonal antibodies. Several products, which are not immunogenic but are nearly as potent as the ricin derivatives, resulted from this effort.

Dr. Sayare emphasized that the initial \$3.5M and an additional \$6M that the company raised was used to fund basic research at Dana-Farber. This is almost \$10M in total and does not include another \$3M in Phase I and

Phase II clinical studies that were undertaken at Dana-Farber, Immunogen's host institution. Dana-Farber did all of the early studies. Immunogen has had 24 different clinical protocols on its first product, Oncolysin B.

Dr. Sayare's next slide described the value derived by Dana-Farber from its collaboration with Immunogen. He noted that the biotechnology industry as a whole has funded academic research for about \$1.5B annually, and referred the Board to David Blumenthal's article in the New England Journal of Medicine, which described the relationships between academia and the industry and the economic benefits derived from this close association. Dr. Sayare indicated that Immunogen files all the patents in its collaboration with Dana-Farber, and Dana-Farber is assigned all of the patents. Immunogen is the licensee for the patents on its ricin derivatives. Dana-Farber will get royalty income when the product eventually gets into the market. Dana-Farber also receives a portion of the royalties Immunogen would receive if it licenses this product to a third party. Also, Dr. Benacerraf received stock in Immunogen at the founding of the company and immediately transferred that stock to Dana-Farber gratis. When the company went public in 1989, Dana-Farber had a windfall of about \$1M. In addition, Dana-Farber benefits from the translational research. Immunogen has provided expertise in areas outside of those which are traditionally held by academic health centers in bringing products to the clinic and Immunogen also collaborated in some of the basic research.

Dr. Sayare showed a slide describing the value derived by Immunogen in its collaboration with Dana-Farber. Immunogen gained ideas and knowledge, including ideas for attaching the monoclonal antibodies to low molecular weight drugs and to plant toxins. Not only did Immunogen gain from Dana-Farber's expertise, some of the leadership of Dana-Farber served as consultants to the company. Immunogen also derives benefit from the clinical trials capabilities of Dana-Farber. Dr. Sayare added that the point made by Dr. Blumenthal in his article is that the money that industry invests in academia is no more productive in terms of sales figures than money that industry puts into its own laboratories. However, through academic collaborations, biotechnology companies gain access to staff that the big pharmaceutical companies do not have access to if they lack these relationships.

Presenting his next slide, Dr. Sayare discussed the value derived by the U.S. taxpayer. Dr. Sayare drew the Board's attention to a calculation done by BIO, which was presented at recent Senate hearings by George Rathmann. The calculation determined that industry-based translational research yields a seven to one leverage of publicly-funded investment in basic research, an enormous benefit to the taxpayer. Without the continued funding of cutting-edge basic research and without this collaboration between the Federal government, academia, and industry, this benefit will disappear.

Dr. Sayare presented a slide discussing the evolution of relationships between academia and the biotechnology industry. He informed the Board that when Immunogen went public in 1989, its stock came at \$10, then immediately sank to \$7. Dr. Sayare expressed that Immunogen probably should not have gone public, but needed the money. Immunogen had raised \$20M of venture capital up to that point, and the venture capitalists were not interested in investing any more money. In 1990, the stock began to rise and went up to \$19. Immunogen sold 2 million more shares at that price and then sold 3 million more at \$17. Although Immunogen raised a lot of money, it was not enough.

In order to raise additional funds, Immunogen looked to big pharmaceutical companies as licensees of its technology. Dr. Sayare explained that many companies are founded as virtual companies, in which research is conducted at places like Dana-Farber, and the manufacturing is done by third parties who have manufacturing capabilities. Immunogen made a \$10M investment in a good manufacturing process (GMP) facility to manufacture its Phase III product.

Dr. Sayare presented another slide, noting that Immunogen also built a relationship with Dana-Farber for another company, Apoptosis Technology, Inc. (ATI), a subsidiary of Immunogen. Immunogen owns about 75 percent, Dana-Farber owns 10 percent, and Imperial Cancer Research Fund owns about 5 percent, and other universities also own a piece. Immunogen created the company to license technology from Dana-Farber, St. Louis University, and other institutions, to build an understanding of apoptotic pathways and to determine whether apoptosis can be turned on in cancer cells in which apoptosis has been turned off, such as by BCL-2 in



**B cell lymphoma.**

**Dr. Sayare concluded that academic science being conducted in the biotech industry is one of the hallmarks of how the industry has evolved. The entire biotechnology industry is different than it was 15 years ago, becoming more of a partner with academia in research, as well as in funding.**

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## **COLLABORATIONS BETWEEN THE NATIONAL CANCER INSTITUTE AND THE BIOTECHNOLOGY INDUSTRY**

**Dr. Wittes announced that he is from the Government and here to help the biotechnology industry. A redefinition or reconsideration of what the Government needs to do in the present environment is required. The biotechnology industry exists because of public investment in fundamental science. Usually when there are symposia in advisory committee settings such as the NCAB, it is appropriate to consider what problems need to be fixed and what opportunities need to be pursued.**

**Dr. Wittes noted that the major opportunity stems from the spectacular explosion of discovery in the pharmaceutical and biotechnology industry. Because of this and because of expectations on the part of the investor community, there is a significant influx of funds into the sector. There is also significant interest on the part of big pharmaceutical companies in little pharmaceutical companies, due to the widespread perception among many large companies that most of the agility and potential for breakthrough innovation exists in the smaller companies in the industry.**

**Dr. Wittes referred to the problems that the Board has heard about today. One of these problems is regulation by the FDA and simplicity by the patent office. Dr. Wittes noted that the Board also heard that these two agencies are responding to what is perceived of as problems and have moved to change patterns of their practice, laws, or regulations. Dr. Wittes added that problems exist in the capital markets with regard to raising money for small companies insure their stability while they attempt to exploit research discoveries. The cost of development is another problem. Also, although there is much volatility within the biotechnology sector of the stock market, the sector as a whole is thriving.**

**Dr. Wittes noted that an interesting feature of the biotechnology sector is the cultural difference compared with a large pharmaceutical company. He speculated that this difference is likely related to the academic provenance of the biotechnology sector, compared to longstanding established companies that are slow to change. Dr. Wittes felt that this cultural difference is important, because it relates to the pace of discovery and the susceptibility to innovation. The downside is that the biotechnology sector is better at innovative science than it is at making drugs out of its discoveries and proceeding through the orderly process of preclinical and clinical development.**

**Dr. Wittes explained that it is against this setting that one asks what the NIH's place is in future liaisons with the biotechnology sector. Dr. Wittes indicated that the small companies have a great interest in developing strategic alliances with larger companies. Small companies receive badly needed influx of capital and can develop comarketing agreements, neither of which are features of collaboration with government. On the other hand, Dr. Wittes commented, interacting with facilities and capabilities that are available at the NCI offers tremendous advantages, such as the clinical trials operation that the NCI funds, both in the new drug development grants and in the Clinical Cooperative Groups. Of the 77 drugs approved for the treatment of cancer in the United States by the FDA, NCI data was important for the approval of about 52 of them.**

**Dr. Wittes stated that, in addition to its history, recent practice confirms the synergy of relationships between pharmaceutical companies and the clinical development programs in the NCI resulting from important differences in the kinds of emphases that exist in these two places. Pharmaceutical companies must be very focused in their drug development. This is particularly true for biotechnology companies, because many of them live or die on the basis of what happens to a single product. Thus, the reduction in risk and the existence of cost**

sharing when a company does business with the NCI can be a tremendous advantage for small companies, in particular. Dr. Wittes noted that these relationships are set up to emphasize collaborative development so that companies do not lose control over pivotal aspects of the development plan.

Dr. Wittes then discussed the justification from the Government's point of view in expending public monies on products that, if successful, are ultimately going to make a profit in the private sector. Although the development of new effective treatments for cancer is an uncertain proposition, it is clearly in the public interest to do the development and it is best done as a public-private partnership. Dr. Wittes stated that there are many reasons for the government to become even more willing to deal with the industry in a partnership arrangement.

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## IMPLICATIONS FOR THE NATIONAL CANCER INSTITUTE

Dr. Mays began by expressing his gratitude to Dr. Klausner for his support. He also recognized Dr. Maria Freire, Director of the NIH Office of Technology Transfer (OTT), for her cooperation and support. Dr. Mays' office is in partnership with Dr. Freire's office, and together they strive to protect the technology and transfer it to the benefit of science and public health.

Dr. Mays explained that the biotechnology industry plays a critical role in the National Cancer Program. Over the past decade, there have been an incredible number of discoveries resulting in new science. Having helped found a biotechnology company in the early 1980s, Dr. Mays saw that the industry's most critical need was certainty. Dr. Mays also has an understanding of the processes in the patent office after spending time there. With these two perspectives, Dr. Mays came to the NCI in the 1990s.

Dr. Mays indicated that there are two contexts in which he would present his information. The first and most important context is that the NCI must fulfill its statutory mission, as opposed to the private sector, where the bottom line is most important. The second context is that although the NCI is not in the private sector, it still must be efficient and cost effective.

Dr. Mays informed the Board that collaboration with the private sector, including the biotechnology industry, is predicated on different statutes. Dr. Mays presentation would focus on only the formal collaboration. He noted that there are many informal collaborations that arise and should continue, as they are an essential part of conducting research.

Dr. Mays acknowledged that the Federal Technology Transfer Act (FTTA) was passed in 1986 and will soon be amended again. Congresswoman Morella had introduced a bill several years ago that has finally cleared both Houses. Dr. Mays provided a summation of the principles of the bill in the Board's materials.

Presenting his first slide, Dr. Mays noted that the most critical point to remember is that as a Federal agency, the NCI can only receive monies under statutory authorities. He provided a list of authorized funds, which include appropriated funds, Cooperative Research and Development Agreement (CRADA) funds under the FTFTA, Gift funds, and Royalty funds. Although all of these funds are important for supporting the work of the Institute, Dr. Mays focused on royalty funds and CRADA funds as the most important.

Dr. Mays explained that most of the data he would be presenting was provided by Mr. John Hartinger of the Financial Management Branch of the NCI, and by Dr. Freire and Mr. Ted Rommel of the OTT. Dr. Mays then showed another slide and indicated that in November 1987, after the FTFTA, the NCI created the Office of Technology Development. Dr. Mays presented data, beginning in fiscal year 1988, to show that royalty funds from licenses were beginning to come in. Royalty funds have continued to increase significantly, as have CRADA funds, particularly with regard to their application in the clinical trial arena. Dr. Mays acknowledged that these significant increases in financial resources are a result of the Technology Transfer Program. Dr.

Mays showed a slide and noted that legislation has been amended to allow royalty funds to be used further for laboratory research, which must be related to increasing the licensing potential.

Dr. Mays presented his next slide and explained that the inventor payments, as required under the law, are at least 15 percent. The NIH provides 25 percent of the first \$50,000 in royalty monies received, 20 percent of the second \$50,000 in royalties, and 15 percent thereafter. The new legislation would increase the cap from \$100,000 to \$150,000 per year per person, and also provide a \$2,000 annual floor. This legislation provides more incentive to the scientists.

Dr. Mays discussed the cost allocations of the NCI Technology Transfer Program. He indicated that the Technology Transfer Fellowship Program is a successful training program, and represents a significant part of the budget of the NCI Office of Technology Development. Other costs associated with the Technology Transfer Program include supporting the NIH OTT, the cost of U.S. patents, foreign patents, and the National Technical Information Service at the Department of the Commerce, the licensing agent in past years.

Dr. Mays showed a slide indicating that although the number of CRADAs executed each fiscal year is relatively small, those CRADAs continue for several years. Thus, the total number of active CRADAs is increasing. Dr. Mays also stated that patent applications and licensing are continuing to increase. Also, because invention disclosure can result in several filings, there are more patent applications filed than invention disclosures. Dr. Mays explained that the NCI has been attempting to reduce the amount of filings to protect its technology more effectively.

To show how the NCI is doing in context, Dr. Mays presented a slide of the Association of University Technology Managers' (AUTM) annual survey. The University of California system is the number one royalty earner, followed by Stanford, Columbia, Michigan State, and the University of Washington/Washington Research Foundation. As an agency, the NCI was not included in the university study but, if it had been, it would be ranked at about number five, followed by Iowa State. Dr. Mays noted that the University of California is proficient in recouping legal costs, and that one entry, Case Western, brought in more reimbursement than legal expenses, which indicated its effectiveness.

Dr. Mays noted that reimbursement of patent costs is an important part of an effective program, and the NCI is working on reconciling its data to present it to the Board. He explained that there is concern that the NCI may be filing too many patent applications. Filing uses a lot of personnel time and financial resources. The NCI is working to reduce its filing rate, which is about 64 percent, to protect its technology more effectively. For fiscal year 1994, Dr. Mays indicated that the University of California system had about a 70 percent filing rate, and commented that many of the large universities with significant royalty incomes are averaging about a 50 percent filing rate.

Recognizing that the NCI can only receive and spend money as legislated, Dr. Mays noted that the NCI can do its job more effectively by ensuring that decisions on intellectual property protection, as well as CRADAs and other technology transfer activities, are more scientifically based. To this end, the NCI is creating small technical review committees of scientists who will provide advice for making scientifically-based decisions on patent filings. Dr. Mays stated that the NCI needs to conserve the valuable financial and personnel resources in the patent licensing program. The NCI needs to use its royalties to accomplish two goals simultaneously. For example, with the Technology Transfer Fellowship Program, the NCI is able to use royalty funds to train scientists and other professionals who are interested in a career in technology transfer. Also, the NCI can give recent graduates the working experience needed in this tight job market and, at the same time, benefit scientists by providing bright, motivated fellows to assist them. Dr. Mays recognized the extraordinary group of staff—Federal employees as well as fellows that serve in the NCI Office of Technology Development.

Dr. Mays continued his discussion, explaining that streamlining is important. Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management, and Dr. Mays' office are working with the Administrative Resource Centers on putting CRADA agreements together and making provisions for the funds so the monies can be used more effectively and the accounting can be tracked more appropriately. Also, the NCI is serving as

a competitive service center for other Institutes in providing resources to assist them, enabling the NCI to use economy of size. Also, the NCI is re delegating the authority to sign some of its Material Transfer Agreements to speed up processes. Dr. Mays indicated that both the NCI and the NIH offices conduct patentability assessments to save money; the NCI computer database system can be used to conduct patentability studies more quickly and economically.

Dr. Mays then turned the focus of his presentation to the creative and aggressive implementation of CRADAs. Dr. Mays stated that there is a need to attract, at an earlier stage of research, appropriate collaborators in the private sector. The selection of collaborators, including both large and small biotechnology and pharmaceutical companies, is important. Selection of collaborators should be based on their skills, resources, advantages, and limitations.

Dr. Mays' next slide depicted a schematic of material transfer agreements. Data from the past couple of fiscal years showed that the NCI is providing significantly more research material than it is receiving. Dr. Mays explained that Ms. Barbara McGary and others at the OTT have been working to create an Material Transfer Agreement (MTA) CRADA, which is a CRADA for the exchange of research materials. This CRADA will speed the process, provide scientists access to materials, and give the biotechnology companies the certainty that they need to leverage future intellectual property rights.

Dr. Mays showed another slide and noted that the NCI has been creative in using the CRADA letter of intent to enable the Institute and the collaborator to immediately begin conducting collaborative research, while lawyers work out the terms of the agreements. Dr. Mays emphasized that the CRADA program is an effort to generate resources and materials to help NCI scientists obtain materials and skills so that their research can progress more quickly. He noted that they also generate money, although this is not their intent. Also, Dr. Mays acknowledged the aggressive marketing and licensing of intellectual property rights as well as effective enforcement of agreements.

In concluding his presentation, Dr. Mays expressed his appreciation to Ms. Guerra for providing copies of a summary of HR2196, Congresswoman Morella's bill, which will give the NCI a couple of tools it has not had before. Implementing the suggestions on how to improve the program, as well meeting the resource needs of the talented researchers in the private sector, will help to make great strides in the National Cancer Program.

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## IMPLICATIONS FOR THE NATIONAL CANCER INSTITUTE QUESTIONS AND ANSWERS

Dr. Schein noted that the speakers today provided the Board with their perspective on the range of complex issues and challenges that face small companies in the field of biotechnology. They also emphasized the potential contribution of these companies to the National Cancer Program. Dr. Schein expressed his and the Board's appreciation for the speakers' informative presentations, noting that they will broaden the perspective of the Board and the NCI and will affect the way business is done at the NCAB in the future. Dr. Schein then invited questions from the Board.

Dr. Freire asked Dr. Sayare to explain his preferred paradigm of the small biotechnology company having to make deals with big pharmaceutical companies to obtain funding. Dr. Sayare expressed his preference to retain the rights to products as much as possible and to permit the biotech company itself to bring them to market. He cited that margins in the pharmaceutical industry are thought to be in the 80 percent range. Although his company's products would not have margins that high, they would be a lot higher than a 10 percent royalty. He noted that recently founded biotechnology companies have funded themselves on the basis of licensing their technology products to large pharmaceutical companies in exchange for near-term cash and 10 percent royalties.

Dr. Freire then inquired whether a biotechnology company should follow the fully integrated model of large

pharmaceutical companies or look for a different model to follow. Dr. Sayare answered that the paradigm that has evolved over the last few years in the face of difficulties in raising funds is one that is more virtual than the vertically integrated pharmaceutical companies that many companies aspired to be in the mid-1980s. Many companies that could prosper during that period, when cash was flowing well, today have looked to big pharmaceutical companies for help. Dr. Sayare noted that the cultural differences he alluded to earlier are important, because biotechnology companies serve as an effective conduit between academia and big pharmaceutical companies. Biotechnology companies can translate basic research into a product and therefore take some of the risk out of the product development process for big pharmaceutical companies.

Dr. Craves commented that there are viable business models for biotechnology companies to form alliances and have a sustainable business, but not necessarily to become vertically integrated. The 1,300 biotechnology companies in the United States and the 700 in Europe cannot all be vertically integrated. There will be a continued drive towards consolidation of the big pharmaceutical companies in the industry because of the need to manage, in an integrated manner, the global regulatory process, the global development process, and global marketing. Dr. Craves explained that biotechnology companies have little ability to compete in the global marketplace, so they must be creative about how to develop sustainable business models and how to align themselves to make that happen.

Dr. Klausner commented on the changes occurring not only in the industry environment, but also in the academic labs. He indicated that most people in an academic lab are thinking about turning their discovery of a protein or protein interaction into a manipulable molecule. An explosion of new ideas and types of products is under way. Dr. Klausner referred to genomics and how it will create ideas for therapeutics as well as diagnostics and detection. He speculated on how the entire enterprise will deal with the demands of expanding clinical research, and asked Dr. Craves about his thoughts on how the industry can deal with the opportunity that the explosion of ideas will create. Dr. Klausner added that the NCI has a big stake in a national infrastructure for clinical trials and asked how it can deal with the biotechnology industry in terms of ideas for products to bring to trials within this infrastructure.

Dr. Craves responded that it is a huge dilemma for the industry. He suggested that becoming more disciplined about assessing preclinical and early clinical studies is a potential solution. Dr. Craves explained that there is a major expense involved in filing the IND and going through Phase I and Phase II studies, and this cost increases significantly with Phase III studies. Being more disciplined about making the right choices early on before a lot of money is spent is prudent. Because of financial considerations, many biotechnology companies felt they did not have options and had to move forward with compounds that, with more financial resources available, might have been evaluated with a different level of intensity.

Dr. Schein referred to issues related to the prioritization of resources. He indicated that only a fraction of eligible patients are being enrolled into clinical trials of new investigative agents. Many trials are being initiated in Europe because of the difficulty of accessing patients in the United States. There is also ongoing competition for ideas; small companies, in particular, have difficulty competing against the large pharmaceutical operations who expend more money per patient and, therefore, use that as a tool for tracking investigators that otherwise might be intrigued by something that has more scientific potential.

Dr. Wittes commented that although the issue of coordination at a national level is part of the problem, it is more a problem of capacity. Much time at the NCI is spent thinking about how to coordinate research, whereas pharmaceutical companies would not like to be coordinated because they do not want their priorities to be in a queue with the priorities of others; they concentrate on satisfying their own priorities.

Dr. Wittes indicated that about 3 percent of adult cancer patients nationally participate in NCI clinical trials. There is much room to expand; however, it is not clear that the clinical investigators are doing innovative early studies with the kinds of products the Board is discussing today.

Dr. Boxer referred to Mr. Poissant's comment that "if it were not for the gold ring, there would be no research." Dr. Boxer also referred to Dr. Mays' comment that "we are not really here to make money; we are

here to do research." Dr. Boxer then indicated that there may be a corporate cultural difference in these two discussions. Dr. Boxer noted that in one of the slides that Dr. Mays showed, it cost \$6.5M for the NCI to make \$11M in profits from the CRADA, whereas it took the University of California \$6M in legal fees to make \$50M in their research. Dr. Boxer commented that there is room for improvement.

Dr. Boxer also asked Mr. Poissant whether there is a problem with biotechnology research patents being broken and imitated in foreign countries that do not respect U.S. patent laws, and then having the products brought back to this country. Mr. Poissant answered that this is a two-part question. In many foreign countries, it is likely that patents are not being honored. He often advises clients not to expend funds to get patents in those countries, particularly on methods and processes, because they are not recognized as an intellectual property. Mr. Poissant added that activity in those countries does not affect the United States, because the Biotechnology Process Patent Act now allows patents on recombinant processes, which blocks the importation of products made abroad by those processes.

Dr. Becker indicated that several issues discussed today concern him, including the litany that one must have a "seamless translation" of research to product; the comment by Dr. Klausner that all scientists immediately see a molecule as a product; and the comment by Mr. Poissant that research would not continue without "a golden ring." Dr. Becker noted that all the products and advances have arisen from investigator-initiated research, which was basic and fundamental in nature, was not directed at products, and was not directed at seamless translation. Dr. Becker commented that he is afraid that centers of excellence--under the guidance of consultants, the seduction of products, and the seduction of stock options--will forget that.

Dr. Becker referred to the September 29, 1995, editorial in Science by Dr. Arthur Kornberg, who indicated that every major advance in medicine, including those that are profitable today, started out in the mind of a scientist who was not thinking about a product. In addition to the clinical researchers, the most precious commodity that is under threat of extinction is the investigator who is studying science in its pure form and asking questions that currently do not seem to have application. Dr. Becker expressed his concern that young scientists might not follow good leads because they may not be commercially applicable, and that they think they should find something seamless to study.

Dr. Klausner responded that the issue of profit is not the same as the issue about research having utility. Dr. Klausner noted that there are important research tools being incorporated into basic laboratories, including his, not to make profit. Many leads are emerging from new technology, and they have nothing to do with a golden ring or whether the research is scientifically motivated.

Dr. Salmon described a cartoon of two scientists in a laboratory looking through the two heads of a binocular microscope; each scientist had a balloon above his head showing what they were thinking about. One had the image of a Nobel Prize medal and the other had a large dollar sign. Dr. Salmon added that motives are sometimes mixed and cannot always be clarified. Dr. Salmon then commented on the biotechnology companies he has worked with over the past 15 years, and noted that for all their incredible expertise in basic science, many are unsophisticated in the area of clinical trials and clinical trial design. Not obtaining enough data in appropriate Phase II trials before moving to Phase III trials, or having a flawed trial design, are reasons some biotechnology companies experience enormous crashes in value.

Dr. Salmon asked Dr. Mays to clarify his comment that different institutes have different policies for their scientists about royalties they receive on inventions, and noted that there is a uniform code within the NIH for patent rights and royalties. Dr. Mays clarified that he stated that the Public Health Service, which is larger than the NIH, has a policy that complies with a statute that only requires 15 percent. However, the Public Health Service goes beyond that to provide 25 percent for the first \$50,000, 20 percent for the second \$50,000, and then 15 percent beyond that, and that this is consistent among the NIH Institutes.

Dr. Sigal commented that the challenge is not to stop the commercialization of science, but to make sure the academic environment has integrity and is free of conflict of interest. The biggest challenge is to save basic science that may not have any commercial applicability. Dr. Sigal expressed that looking for intellectual

property and commercialization is becoming a serious problem, and that pure philanthropic giving for basic research and diseases of interest is changing, even at Cancer Centers.

Dr. Freeman inquired about the ultimate implication of the private ownership of 100,000 genes in the human genome, and the tests that can be done on them. Dr. Klausner responded that the issue of patenting sequences is problematic. He explained that it is important to ensure that the entire human genome sequence is in the open database, and that he is working to couple with organizations that will sequence important regions of the genome and put them onto the Internet, as was done with BRCA2.

Dr. Klausner noted that it will be interesting to observe whether there are any differences in the development of tests for BRCA1, which has a sequence that was patented, and BRCA2, which was a sequence available on the Internet. Dr. Klausner guessed that there would be no difference in interest by companies despite the fact that one represents a human genome sequence that is freely available. Dr. Klausner expressed his hope that information will be openly available, because it is discouraging to recognize how much data on the genome is being developed at private companies and is not available. Dr. Klausner added that the only way to deal with this issue is to steer funding towards entities that will put the information into the public domain.

Dr. Day noted that there is a unique genetic composition that each body contains, but it cannot be proprietary if one generalizes. Dr. Schein commented that there could be better coordinated efforts and flow of information that might allow for less duplication and more efficiency within the system. However, this would come with certain controls and perhaps some disincentives that might not attract as many scientists into the process. At the same time, the free enterprise system, as it exists in this country, works. Dr. Schein stated that for research to have an impact on the major mission will require development, regulatory approvals, and eventually commercialization to bring it to the widest possible audience. He indicated that the way in which this balance is achieved needs to be discussed.

Dr. Schein referred to Dr. Klausner's comments that there is an explosion of discovery going on, and that the private sector is playing a more visible and potentially more important role than it had in the past. The team of academic centers, the NIH, and the private sector, including small companies, which are the seedbeds of innovation, must be brought together to encourage continued contributions. Dr. Schein thanked the speakers, the Board, and the extended audience for their contributions.

Dr. Rimer announced that the Subcommittee on Cancer Centers would be meeting momentarily and then adjourned the first day of the full NCAB meeting.

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## **HORMONE REPLACEMENT THERAPY (HRT) MINI-SYMPOSIUM**

Dr. Rimer convened day two of the 97th NCAB meeting with a brief overview of the day's business. To introduce the mini-symposium, Dr. Rimer characterized hormone replacement therapy (HRT) as one of the nation's great current medical controversies because of unanswered questions about estrogen replacement therapy (ERT) in general and, most importantly for the NCAB, about which subset of women should receive it. She noted, as evidence of the widespread interest in the topic, its prominence in women's conversations as a significant decision point in their lives, in the popular media (e.g., the cover of Time), and on the Internet. Dr. Rimer commented that although HRT has been regarded as an issue to be addressed by other Institutes, members of the Board, consumers, and providers alike see it also as a cancer issue. The scope of the issue is immense, with estimates that one quarter of the women in the United States are at or past menopause and with millions more (the baby boomers) approaching menopause. The potential benefit of HRT for reducing the risk of heart disease and osteoporosis has been widely reported; however, the potential risk for cancer has mitigated enthusiasm among the medical community and public. Yet, very little study has been done of the cancer aspect of HRT (as borne out by a search through the NIH grant portfolio) and of women's perceptions and preferences related to HRT (the work of Dr. Lila Nachtigall, symposium speaker, is a notable exception). Dr. Rimer pointed out that the issue is of great importance to women and providers because of the challenges to decisionmaking posed by the trade-offs of health risk and benefits, the types and doses of therapies available, and the potential

alternatives to HRT. She commended the work of Ms. Mayer and Ms. Iris Schneider in organizing the mini-symposium and introduced Ms. Mayer to present background comments on the symposium.

Ms. Mayer acknowledged the work of Ms. Schneider and all others who helped organize this and an earlier symposium on quality-of-life issues. She traced her interest in HRT to her work in a diagnostic breast clinic where patients at high risk for breast cancer regularly deal with conflicting advice about the initiation of HRT from their gynecologists and oncologists. She referred Board members to a summary of NIH awards by mechanism and category that showed more than \$20M is spent on HRT research. Ms. Mayer indicated that the goal of the symposium is to understand what is known about HRT and identify gaps in knowledge and possible mechanisms for closing the gaps. She listed the symposium speakers and their particular focuses: Dr. Meir Stampfer, Harvard School of Public Health--Risks and Benefits of HRT; Dr. Jacques Rossouw, The NIH Office of Disease Prevention--The HRT Component of the NIH Women's Health Initiative; Dr. Jeffery Perlman, The NCI Community Oncology and Rehabilitation Program--HRT in Breast Cancer Survivors; and Dr. Nachtigall, New York University School of Medicine--HRT Decisionmaking Interaction Between a Woman and Her Healthcare Provider.

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## RISKS AND BENEFITS OF HRT

Dr. Stampfer prefaced his broad overview of the topic "Weighing the Risks and Benefits of HRT" by noting that part of the researcher's job is to make it easier for women to make this difficult medical decision. He expressed uncertainty as to whether decisionmaking had been made easier or harder so far.

Dr. Stampfer reviewed the history of HRT research, which began in 1975 when it was shown that postmenopausal hormones raised the risk of endometrial cancer. Later studies showed that the relative risk estimates for increased risk of endometrial cancer were greatest in the early stage and that the cancers were lower grade and less likely to be lethal. Dr. Stampfer noted that common practice currently is to administer progesterin to women with an intact uterus, which reduces the risk of HRT to baseline or lower.

Dr. Stampfer then reviewed what is known about the effects of HRT on osteoporosis, which is a major public health problem in that about one in three women will experience an osteoporotic fracture by age 80. Studies have established the effectiveness of estrogen in stopping postmenopausal bone loss, an effect that is noticeable from the beginning of treatment; the same studies have shown that women receiving placebo experience a continuing decline in bone mineral content. In studies where there is a crossover after a certain period, women randomized to the estrogen group continue to maintain bone as long as they take estrogen, but immediately start losing bone when switched to placebo. In contrast, women randomized to the placebo group maintain bone at the point where they were when the switch to estrogen occurred. Dr. Stampfer stressed the fact that the effect of estrogen in maintaining bone density is immediate, but that estrogen acts at the stage of bone loss that is present at the time. Therefore, estrogen given far past the onset of menopause will not bring about a return of bone that had been lost. Dr. Stampfer cited several studies which show that the bone-sparing effect of HRT reduces the risk of osteoporotic fracture by half.

Dr. Stampfer stated that the principal long-term benefit of estrogen from a public health perspective appears to be in reducing the risk of heart disease. Using a slide to summarize recent prospective studies of estrogen and heart disease, Dr. Stampfer pointed out that all but one showed a relative risk below one, suggesting the benefit of reduced risk of heart disease among estrogen users. A reanalysis of data from the study with a higher relative risk—the Framingham study—also showed a benefit. Dr. Stampfer noted, therefore, that these studies of HRT and heart disease point in the same direction, a remarkable epidemiologic consistency.

Dr. Stampfer summarized the Nurse's Health Study, an observational study founded under the leadership of Dr. Frank Speizer. It comprises 121,700 U.S. female registered nurses who responded to a questionnaire in 1976. Since then, the cohort has been followed by means of a questionnaire every 2 years to update a wide array of information about lifestyle practices such as diet, physical activity, and medication use. When a disease



endpoint is reported, the investigators obtain the woman's medical records to confirm the diagnosis. Disease endpoints of interest include heart disease, cancer, diabetes, fractures, and many others. Now in its 20th year, the study has achieved 90 percent follow-up from the dedicated and conscientious nurses. A companion study—Nurse's Health Study II—was founded in 1989, with 116,000 women participating. Together, the two cohorts comprise about 235,000 women, making this the largest ongoing longitudinal study of women's health.

Dr. Stampfer reported that an analysis of the effect of estrogen use on the risk of heart disease in the Nurse's Health Study populations (with hard endpoints of fatal or nonfatal myocardial infarction) showed a relative risk of 0.56 among current users, which corresponds to a 44 percent reduction in the risk of coronary disease. Past users had a trend towards reduced risk, but it was not statistically significant. Similarly, an analysis of cardiovascular death in this cohort revealed about a 40 percent reduction in risk of death. Because estrogen users see physicians more frequently and tend to be healthier than nonusers, the investigators recognized the need to adjust for minor differences in the distribution of risk factors. Therefore, they analyzed subgroups of estrogen users in these two categories and still found a reduction by half in their relative risk for heart disease compared with nonusers. These findings were borne out in a meta-analysis of all the studies for current estrogen use; Dr. Stampfer showed the results of the meta-analysis using a slide.

Dr. Stampfer noted the concern in recent years that the addition of progestins may attenuate the benefit of reduced risk for heart disease because of their potential for adverse effects on vascular contractility and lipids. He reported that recent investigations in the Nurse's Health Study produced no evidence to support that fear. In fact, it was found that the relative risk for estrogen plus progestin use was also significantly lower. Dr. Stampfer listed plausible biological mechanisms to support this observation: estrogens have beneficial effects on lipids, promote vasodilatation and improved blood flow, reduce low-density lipoprotein (LDL) uptake to the vessel wall, and act as antioxidants for LDL. He added that animal studies have supported this finding.

Turning next to a review of risks associated with HRT, Dr. Stampfer noted that the fear of breast cancer is the primary reason women discontinue HRT. He reviewed reasons why there is a plausible link between estrogen and breast cancer. Known risk factors for breast cancer that are related to endogenous estrogens include age of menarche, age at first birth, parity, age at menopause, term delivery, and obesity. Using a slide showing the age distribution of incidence of breast cancer, Dr. Stampfer pointed out that the rate of breast cancer incidence increases sharply in the premenopausal years and levels off at the time of menopause, which marks a change in hormonal milieu. The incidence of breast cancer increases with age, but the rate of increase slows. Therefore, the older a woman is at the onset of menopause, the higher her risk of breast cancer. Dr. Stampfer explained that mathematical modeling of that relationship shows a small but statistically significant increase of about 4 percent in risk of breast cancer with each increasing year of premenopausal status, which translates to a 20 percent increase over a 5-year period. This causes concern that giving women estrogen mimics the premenopausal state and therefore maintains the higher trajectory for increased risk of breast cancer. He noted further that animal studies show that estrogen can serve as a promoter of tumor growth, and estrogen receptors can be found in many of the tumors, all of which points to a biological plausibility for the link between estrogens and breast cancer.

Dr. Stampfer reported that epidemiologists have found no increase in risk of breast cancer when all estrogen users are combined and compared with those who never used estrogen, but he noted that this evidence fails to distinguish between two important subgroups—those who have used estrogen for a long duration and those who have used estrogen for as little as a few months.

Noting that the greater concern is for the effect of longer-term use, Dr. Stampfer reported the findings of several meta-analyses combining studies that evaluated relative risk to duration of use: a relative risk of about 1.23 for 10 or more years of estrogen use; somewhat greater relative risk for 15 or more years of use; and relative risk of about 1.5 for 20 or more years of use. He pointed out, however, that the meta-analyses show a trend of wider confidence intervals over time because of the lack of data on very long-term followup of women. Dr. Stampfer suggested that this information gap causes concern if one is going to consider very long-term use of estrogens.

Dr. Stampfer next presented the findings from studies of current users of estrogen, the other group of particular interest. He reported that the meta-analysis summarizing the few studies that distinguished "current use" from "ever use" show no increase in risk for the "ever use" group but a 40 percent increase in risk, with some duration effect, for current users. These issues were examined in the Nurse's Health Study, which represents followup from 1976 to 1992 (about 374,000 person years) in postmenopausal women. No apparent increase in risk occurs in the first few years, but risk increases as duration increases, and by 5 years duration or longer, the increase in risk is a statistically significant 36 percent. For 10 years duration or more, the increase in risk is 47 percent. In contrast, no significant increase in risk was seen in women with 10 or more years of use in the past, leading investigators to suspect that estrogen works primarily as a very late-stage promoter of growth of a tumor that is already present. Dr. Stampfer concluded that these analyses based on followup in the Nurse's Health Study do show an increase in breast cancer mortality with estrogen use. Of additional concern is the finding that the relative risk for breast cancer seemed to go up with increasing age. This greatly complicates the attempt to balance risks and benefits in the decisionmaking process, because it is the older age group that derives the greatest benefit from HRT in reduced risk for heart disease and reduced incidence of osteoporotic fracture.

Dr. Stampfer reviewed types of information that can be used in risk and benefit assessment for long-term estrogen use, such as mortality. The Nurse's Health Study shows that coronary heart disease (CHD) is the more common cause of death in women overall, but breast cancer is more important numerically as a cause of death in younger ages. CHD overtakes breast cancer as the primary cause of death in the middle years (55 to 59). Further complicating the risk-benefit assessment for decisionmaking purposes is the identification of many risk factors for CHD that are modifiable and can lower a woman's risk of CHD; in comparison, very few ways are known for reducing the risk of breast cancer. Dr. Stampfer concluded that although benefits for HRT do outweigh the risks on the average, each woman together with her physician must develop her own risk profile to arrive at her own decision about HRT. He noted that other effects of estrogen can be considered in a risk-benefit equation, namely, the symptomatic benefits of HRT for menopausal symptoms and the emerging evidence that estrogen may have a beneficial effect on cognitive functioning. Dr. Stampfer indicated that confirmation of the cognitive functioning benefit would radically change the risk-benefit equation, and that the list of NCI grants shows great interest in support for the study of this theory.

Dr. Stampfer stated that looking at studies with mortality as an endpoint has the advantage of relative simplicity as a means of judging the net effect of estrogens except that this method ignores important quality-of-life issues, and the analysis of relative risk must be interpreted carefully to account for bias caused by the fact that women discontinue estrogen if cancer is diagnosed. As other sources of information for assessing risks and benefits of HRT, he listed the important studies and trials in progress, such as the HERS trial of secondary prevention of cardiovascular disease and the NIH Women's Health Initiative. Randomized trials are important to rule out the problems of confounding and selection found in observational studies.

Dr. Stampfer concluded his presentation by identifying the kind of information that needs to be gathered to balance risks and benefits: precise estimates (with tight confidence intervals) of the effects of HRT; effects of HRT in subgroups to ascertain those groups that benefit from estrogen therapy; information about the effects of different formulations of hormones that women use; and information on very long-term effects. To obtain the latter, he noted, it will be necessary to extend followup in observational studies for long periods.

Dr. Stampfer closed with a plea for recognition of the importance of using a variety of sources of data to assess risks and benefits: biological studies to understand the mechanism; randomized trials to rule out selection bias; and long-term, large observational studies.

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## THE HRT COMPONENT OF THE NIH WOMEN'S HEALTH INITIATIVE

Dr. Rossouw began with an introductory review of the organization of the Women's Health Initiative (WHI).

The WHI is the overall title for a randomized, double-blind clinical trial with many components: a trial of HRT, a trial of a low-fat dietary pattern to prevent breast cancer and colorectal cancer, and a trial of calcium and vitamin D to prevent osteoporotic fractures. WHI also includes an observational study beyond the trials. Primary outcomes to be studied are CHD, breast cancer, colorectal cancer, and osteoporotic fractures, with CHD as the most important outcome because it has the highest mortality rate in older women.

Dr. Rossouw reviewed the rationale for continuing to study the benefits and risks of HRT in reducing CHD. He reiterated and agreed with Dr. Stampfer's earlier contention that, although the data from many observational studies are consistent and strongly suggest there is a risk reduction of 40 to 50 percent, these data may also be consistently confounded. The observational data, therefore, cannot be used in themselves as a basis for prescribing hormones en masse to postmenopausal women. The observational studies also indicate that HRT appears to mediate a risk reduction for CHD in current users, those with surgical menopause, nonsmokers, and those with preexisting heart disease. However, these studies are based on old data, Dr. Rossouw noted, and estrogen dosages are lower than in the past, long-term treatment is being initiated more frequently, and combination treatment for women with intact uteruses has become a norm, but was not so in the past. He added that there is concern that differences may exist between users and nonusers, as Dr. Stampfer noted when he presented mortality data showing that prevalent disease will remove a woman from a pool of estrogen users and therefore improve the relative risk figure for the user cohort. Finally, Dr. Rossouw reviewed the potential biologic mediators of an estrogen effect on the vascular system, which also affirmed that the beneficial effect of HRT on CHD is plausible.

Dr. Rossouw stated, on the other hand, that risk for breast cancer cannot be dismissed because of the biological plausibility and lack of precise estimates of risk for the long-term and "current use" subgroups, as indicated by Dr. Stampfer, even though observational studies show no significant breast cancer risk for "ever use" of hormones. Moreover, European studies tend to show an increased risk for breast cancer.

Dr. Rossouw observed that there is a lesser degree of consistency for the hormone and breast cancer association in observational studies than for the hormone and CHD association. He gave the example of the Nurse's Health Study, which suggested an increased risk for current users of hormones (either unopposed or in combination) for 5 or more years but did not show an increased risk for past hormone use. He compared these findings with those from the study at the Fred Hutchinson Cancer Research Center, which were consistent with the Nurse's Study for "ever use" but diverged in the "current use" cohort in that they did not show an increased risk.

Dr. Rossouw then reviewed the history of hormone use and the various factors that have influenced the use and pattern of use over the decades. In the 1960's or "feminine forever" era, enthusiasm for hormone use in older women mediated a sharp increase in number of prescriptions. The upward trend during that time was not tempered by the observations that estrogen in men did not prevent but actually increased heart disease (albeit in doses that were higher than currently used) and that oral contraceptives (OCs), again in higher doses, tended to increase heart disease. In the mid-1970s, it was observed that estrogens were associated with an increase in incidence of endometrial cancer, and the number of prescriptions dropped dramatically. In the late 1970s and early 1980s, it was found that the addition of progestins appeared to obviate the risk of endometrial cancer, and the number of prescriptions for progestins increased for women with a uterus. Simultaneously, because of emerging evidence that estrogen may lower CHD risk and prevent bone loss and fractures, the number of prescriptions for estrogens, now often in combination with progestins, began steadily rising and has apparently continued to rise. Dr. Rossouw noted that the observation that estrogens cause breast cancer does not seem to have stemmed the enthusiasm for using them. He added that, in the current era, investigators are working to assess the benefit versus risk of using hormones and that is the thrust of the WHI. Dr. Rossouw pointed out that although WHI has a primary outcome of CHD, the study algorithm is fashioned for overall benefit versus risk assessment.

Dr. Rossouw reported that a recent survey by the National Heart, Lung, and Blood Institute (NHLBI) found that 82 percent of cardiologists, internists, family practitioners, and general practitioners (excluding gynecologists) reported that they prescribed hormones. Most prescribed them for relief of menopausal symptoms (93 percent) and for osteoporosis (91 percent). Dr. Rossouw noted, however, that about 66 percent

also prescribed hormones to prevent CHD and 44 percent prescribed them to treat high cholesterol even though effective and demonstrably safer treatments exist for both of these conditions. He observed that these findings confirm the need for clinical trials such as HERS and WHI to answer questions that observational studies cannot answer: Is it estrogen or other characteristics of estrogen users that explains the apparently lower risk? To what extent do progestins modulate the effect of estrogens? Dr. Rossouw contended that intermediate outcome trials also do not suffice, and he cited examples to support this contention. He stated that clinical trials are needed to answer questions about the long-term safety of estrogen: What is the real risk of cancer of the breast or uterus with long-term treatment? Will endometrial cancer risk be prevented over the longer term with a combination? What is the risk for other conditions such as thromboembolism and gallstones?

Dr. Rossouw stated that the WHI clinical trial is based on the belief that heart disease, cancer, and osteoporotic fractures are so important to public health that nothing less than certainty is needed before a public health statement or guidelines to physicians can be given. Randomized clinical trials are the gold standard. Study questions for the HRT component of the study are as follows: Does estrogen or estrogen with progestin prevent CHD, prevent osteoporotic fractures, or increase breast cancer? What are the overall risks and benefits? Should most postmenopausal women take hormones?

Dr. Rossouw reported that 40 centers across the nation are recruiting women for the clinical trial. So far, 7,500 women have been recruited for the hormone component; the goal is 27,500, and recruitment will continue until spring 1998. The study drugs are the conjugated equine estrogen premarin at 0.625 mg daily alone for women without a uterus, estrogen in combination with medroxy progestin at 2.5 mg daily, or matching placebos. The study design envisions 6,000 women in each arm of the estrogen-alone study and 7,500 women in each arm of the estrogen plus progestin study. In all, 27,500 women will be followed for an average of 9 years—some as few as 8 years and others for 12 years.

Dr. Rossouw displayed a slide itemizing statistical power based on assumptions of effect size (size after allowing for attrition, loss to followup, noncompliance) for the outcomes of heart disease, all fractures, hip fractures, and breast cancer. The power at a two-sided  $p$  of less than 0.05 for estrogen-alone treatment is over 80 percent for the primary outcome of CHD, 99 percent for all fractures, 65 percent for hip fractures, and 46 percent for breast cancer over the 9-year followup. If the followup is extended as anticipated, pending the availability of funding, the power to detect the primary outcome of breast cancer would increase to almost 80 percent. Dr. Rossouw noted that the power for the combination therapy for breast cancer is more robust because the sample size is larger. He reported that the protocol includes plans to do an analysis for breast cancer combining the estrogen and the combination therapies. The combined therapies versus placebo would provide more than 80 percent power to detect an effect on breast cancer within the planned trial duration. He defended the plan to combine therapies as being reasonable because the observational data appear to show consistent effects for the single hormone versus the estrogen-progestin combination.

Dr. Rossouw also reported much interest in studying biological mechanisms within the clinical trial, which will involve obtaining blood samples at baseline and at various intervals. By examining changes in blood variables in the active versus control arms, the investigators expect to begin to learn about potential mechanisms that may explain the differences in survival. However, this method is not conclusive. Dr. Rossouw stated that the possibility also exists for looking at mechanisms within the active treatment cohort, and he explained the methodology for such a prospective case-control study. The analysis of intermediate variables in cases versus controls in the active treatment group could provide information about the extent to which the treatment effect on a particular blood variable affects the disease outcome. Dr. Rossouw noted that this methodology is most immediately applicable to cardiovascular outcomes and would be applicable to cancer outcomes if appropriate intermediate variables can be identified.

Dr. Rossouw summarized the public health point-of-view as it relates to WHI. HRT cannot be endorsed for life-long treatment for prevention of CHD until the study results are available. He observed that the short-term treatment for menopausal symptoms is a registered and proven indication, and there is no indication for adverse effects over the short term (less than 5 years). Long-term HRT treatment for osteoporosis diagnosis is approved and registered with the FDA. Dr. Rossouw commented, however, that a new drug alendronate has been

approved as an alternative treatment for osteoporosis and may be preferable. He pointed out that good treatments exist to prevent CHD in men and women, including aspirin, which was definitively proven in clinical trials in women; beta blockers, which are effective in secondary prevention; and cholesterol lowering, which is effective in both sexes in secondary prevention. In conclusion, Dr. Rossouw expressed concern that the medical profession is rushing to judgment about HRT, and he cautioned against current trends. He advocated adherence to evidence-based medicine in situations where there are important public health questions.

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## HRT IN BREAST CANCER SURVIVORS

Dr. Perlman, Program Director in the Division of Cancer Prevention and Control (DCPC) Community Oncology and Rehabilitation Program, began his presentation with the background information that the WHI was launched at the time when interest in studying breast cancer was at the maximum. He commented that the long period before questions about breast cancer and hormones would be answered and the exclusion of breast cancer survivors from the study were sources of disappointment. About the time WHI began, DCPC received four research concepts from the Cooperative Oncology Groups to study HRT in breast cancer survivors. The groups serve as research bases for DCPC's Community Clinical Oncology Program (CCOP). Two of the concepts proposed to investigate the role of hormones on quality-of-life in a population of 20,000 women and the impact of hormones on their underlying disease. To review these concepts, DCPC convened a working group of oncologists, gynecologists, gynecologic oncologists, reproductive endocrinologists, and epidemiologists. The conferees task was to consider whether enough data existed about hormone safety in healthy women to allow the systematic investigation in women with cancer. When safety could be assured, the conferees could consider the central question of what combination of hormonal agents would be suitable for study for which breast cancer survivors and for which of the clinical indications.

Dr. Perlman indicated that the review was complicated by the need to consider multiple safety issues and to compare the efficacy of multiple drug combinations. To that end, the reviewers addressed questions such as what is known about ERT in survivors and in healthy women; what is known about HRT in general; how tamoxifen complicates the issue; what studies could be proposed as first investigations; and what to do with patients until some of these questions could be answered.

In the quest for information about ERT, the two major areas of review were (1) consideration of the clinical indications and approved use of ERT by healthy women, and (2) comparison of the various progestogens for their level of endometrial protection and symptom control in healthy women. The data for normal women were used as a measurement of safety and to balance risks and benefits, and statistical models were developed for low-risk versus high-risk women to see if measures of safety were similar and to determine whether a particular area was reasonable for investigation. As a result of their consideration of both the natural and synthetic estrogens in current use, the working group concluded that premarin, the most widely used in both classes, would be a good agent, but they agreed that any of the natural estrogens would be reasonable for clinical trials.

Approved or widely accepted indications for ERT are as follows: ERT has received FDA approval for relief of the symptoms hot flashes and vaginal atrophy and for prevention of osteoporosis; ERT is partly established and widely accepted for relief of the symptoms skin wrinkling and psychological distress and for prevention of CHD. The working group concluded, therefore, that the reasonable focus of long-term trials would be symptoms rather than prevention of CHD or osteoporosis in women with breast cancer. The reviewers also recommended the use of premarin because of the 30 years of experience using this formulation. The use of any other estrogen formulation would require equivalency studies and add an extra burden of research.

Dr. Perlman reported that the review of HRT and the progestogens was complicated by differing opinions about progestogens. Some thought they were necessary for all women with a uterus; others thought that premarin mediated endometrial atrophy in enough women who used it that adding progestogens was not worth the risk because of their unknown and unquantified effects to the breast. Adding to the confusion were the findings that progestational agents vary in their pharmacology and metabolic and side effects and none has been approved

for HRT at this time. The working group selected medroxyprogesterone acetate (MPA), which is derived directly from progesterone, as being the most reasonable to use in clinical trials should such trials be approved. MPA was selected because it requires a lower dosage than some other progestogens and it has almost no estrogenic and androgenic side effects. Dr. Perlman noted, however, that the working group approved MPA with the provision that, if clinical trials in breast cancer patients became a reality, research would include studies on MPA's effect on breast biomarkers.

The last area of review with the data from healthy women was the development of statistical models to assess the risks and benefits of hormone use in women at the various risk levels. The goal was to see if women at the highest levels of risk for breast cancer had substantially different safety profiles for hormone use and to answer the question: Does long-term ERT or HRT make sense for women at high risk for breast cancer, let alone women who already had the disease? Dr. Perlman noted that the results were reassuring. Using a table showing estimated change in life expectancy for 50-year-old white women by risk status, he pointed out substantial life expectancy gains for normal women and women with prior CHD risks on both ERT and HRT. The slide also indicated that less benefit was anticipated for women with a family history of breast cancer.

Dr. Perlman reported that DCPC, with the help of Health Decisions, has recently run models using the assumption that women had a fivefold increase in breast cancer. They found no change in life expectancy for ERT and almost no change for HRT. This was considered reassuring in that if hormones could be used in women even with a fivefold breast cancer risk, it was reasonable to proceed with investigations in this area. With results that were considered reassuring from both sets of statistical models, the decision was made to concentrate on the area of hormones and breast cancer.

Dr. Perlman reported that the working group first considered analytic and well designed basic science and epidemiologic studies. They found information about estrogens and progestogens in experimental animal models, human tumor cell models, and from major breast cancer epidemiologic investigations. The review helped establish the safety of hormones for short-term studies in breast cancer patients. For example, from review of data about estrogen and progesterone in experimental animal breast carcinogenesis systems, it appeared that all ovarian hormones and their derivatives are potential carcinogens, but hormonal carcinogenesis requires long induction periods. Therefore, short-term studies using low doses of hormone seemed reasonable. Additional studies using chemical carcinogens and hormones and studies of hormones alone showed that estrogen is always necessary but not sufficient by itself to induce tumors. The studies gave one clue that high-dose progesterone used very early in life in the animal models may actually counter the estrogen effect, leading the reviewers to postulate that progestogens used at a proper dose might actually be a useful adjunct for reducing both breast and endometrial cancer risk.

The working group then considered the human tumor cell system and biomarker studies and came away with less confidence that hormones can be used safely in breast cancer survivors and with the sense that HRT might not be as safe as ERT. Dr. Perlman noted that, although it is difficult to separate the role of progestogens from that of estrogens, there are enough common estrogen plus progestogen effects on growth factors, oncogenes, and cellular proteins to suggest that the roles may be additive. This created some concern about deciding to use HRT in breast cancer patients. Subsequently, a major finding reported by Robert Dixon indicated that estrogen and progestogens, because they affect the early stages of carcinogenesis rather than the later stages of progression of metastases, might actually affect primary or second primary tumors more than they would affect recurrences.

Dr. Perlman showed a slide summarizing meta-analyses of the effect of ERT on the risk of breast cancer to reemphasize the point that overall the relative risk is not great. However, the meta-analyses from Steinberg and Grady indicated a relative risk of 1.3 (or 30 percent increase) for long-term users, suggesting that long-term investigations should be avoided for now for breast cancer survivors. Dr. Perlman commented that the issue of a potential 30 percent increase in breast cancer in women participating in trials for symptom relief would have to be addressed.

Using a slide summarizing data from three of the few epidemiologic studies that distinguish between ERT and

HRT effects, Dr. Perlman pointed out that the relative risk for estrogen plus progestogen is usually greater and never less than that for estrogen alone. These findings reinforced the reservation about using progestogens with estrogen in people at high risk for breast cancer and people with a history of the disease.

Finally, Dr. Perlman noted, the committee dealt with the issue of what information was available about breast cancer patients who are exposed to hormones. Fear of using hormones was quantified in terms of recurrences of second primary tumors, and breast cancer treatment studies were examined for underlying rates. The working group also considered the use of tamoxifen as a replacement for ERT, taking into account its safety and comfort concerns. Lastly, the working group reviewed the limited clinical evidence as to what happens when breast cancer patients are exposed to hormones during or after the advent of their disease.

Dr. Perlman presented data summarizing the number of new cases in excess of the current rate that could be expected if the use of hormones mediated a 30 percent increase in breast cancer. Figures (rate per 1,000) representing the occurrence of primary breast tumors in normal women came from the Surveillance Epidemiology and End Results (SEER) registry, and figures representing the occurrence of second primary tumors in breast cancer patients and for all recurrences in breast cancer survivors came from the National Surgical Adjuvant Breast and Bowel Program (NSABP) breast cancer treatment trials. In normal women, only one new case of breast cancer (per 1,000 women) due to hormones would be expected to occur per year, which would be an acceptable risk given the reductions in CHD and osteoporotic fractures. However, if hormones affect only second primary tumors, 2 percent of women would be adversely affected over 5 years. Acceptance of this level of risk by the review committee was mixed in spite of the known benefits. Dr. Perlman reported that it was the alarming rate of increase that could be expected for all recurrences in breast cancer survivors (including second primary tumors), which amounted to 10 percent after 5 years or 12 to 18 cases of new active disease per 1,000 per year, that led the committee to change directions.

Dr. Perlman stated that a proposal for a clinical trial was presented by Charles Loprinzi, one of the CCOP investigators. The trial compared tamoxifen plus the progestogen megestrol to tamoxifen alone for the purpose of symptom relief. A review of the data showed that tamoxifen may have additional beneficial effects to bone and heart, much like the effects attributed to estrogen, and that the addition of megestrol could serve as a progestogen to protect the endometrium. On the basis of these findings, the committee considered that using the combination of tamoxifen with another progestogen would be the more reasonable direction for breast cancer survivor studies.

Dr. Perlman noted, however, that some reviewers continued to believe that a trial of HRT in its present formulation should be studied in breast cancer survivors. Information to support this belief came from the results of a 12-year clinical series conducted in Southern California involving 77 breast cancer survivors. Half of the patients received HRT, the other half received ERT, and no difference in recurrence rates was seen. This investigation was regarded as a suitable Phase I toxicity study for ERT and HRT. It led to the conclusion that Phase II studies focusing on both safety and efficacy and involving a few hundred patients could be sponsored as long as known combinations of hormones were used--standard ERT, standard HRT, or tamoxifen plus a progestogen.

Dr. Perlman reported that another set of data helped make the case for a trial of standard ERT or HRT--circumstantial safety information from a series of small clinical studies. The studies produced no evidence of any differences between a high-hormone situation and a low-hormone situation in pregnant women with breast cancer, women who became pregnant subsequent to breast cancer, women who had used OCs subsequent to breast cancer, and women who had breast cancer subsequent to ERT use.

On the basis of these reviews, the working group came to the following conclusions for clinical studies: (1) It is important to study HRT and ERT in a controlled manner in breast cancer patients before they become commonly used in the medical practice; and (2) Short-term clinical trials should be initiated to select optimum drugs and establish safety to the breast.

Regarding the treatment of breast cancer patients until clinical trials are completed, Dr. Perlman stated that

short-term use of the drugs seemed reasonable based on data presented by Dr. Stampfer and others. Long-term use may be unwise, and clinicians were advised to consider alternative therapies for symptom relief.

Conclusions on study design and endpoints reached by the working group were that small randomized Phase II clinical studies were recommended with a focus on relief of menopausal symptomatology. In this regard, Dr. Perlman noted, concepts for two studies have been approved. The studies would accommodate women already on adjuvant tamoxifen by adding a progestogen to relieve hot flashes. The working group also recommended that studies should be designed to produce information on breast and endometrial proliferative effects; to examine patient acceptability and convenience and quality-of-life issues; and to focus on providing information on progestogens and breast intermediate biomarkers.

In concluding his presentation on HRT in breast cancer survivors, Dr. Perlman gave a brief summary of progress and lack of progress in recent years. He pointed out that although DCPC had received recommendations from the cooperative groups for 20,000-person clinical trials of HRT, no trials using standard HRT therapy in breast cancer survivors have been initiated in the intervening 2 -years. All studies have investigated tamoxifen plus MPA, except for one small arm in one trial that will be a Phase I study of estrogen plus tamoxifen in women without a uterus.

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## THE HRT DECISION-MAKING INTERACTION BETWEEN A WOMAN AND HER HEALTHCARE PROVIDER

Dr. Nachtigall thanked symposium organizers for the invitation to talk about interactions between the physician and patient about hormone replacement, noting that she drew from 28 years of experience in this area. In these interactions, the patient decides whether to start HRT, whether HRT should be short- or long-term, and what route to use. Dr. Nachtigall emphasized the importance of differentiating between long- and short-term therapy, citing the general accord that exists about short-term therapy. She stated that long-term therapy, on the other hand, is one of the most important issues that is discussed by a woman and her physician. Rather than tell a patient at the outset that she is going on long-term therapy, most physicians will discuss the risks and benefits with the patient initially and review them at least once a year thereafter, as well as evaluate new developments in hormones. Dr. Nachtigall acknowledged that physicians depend on epidemiologists for the most current information.

Dr. Nachtigall stated that physicians must evaluate the patient's condition in all stages of menopause and differentiate between what is an estrogen effect and what is an effect of aging. In the late stage, for example, 75 percent of osteoporosis in women is attributable to postmenopausal estrogen deficiency. Bladder symptoms and heart disease are more complicated, because they take aging and other factors into effect. In early stages, vasomotor symptoms comprising the menopausal syndrome include hot flashes, night sweats, and chills, but, according to Dr. Nachtigall, it is hot flashes that bring a patient into the doctor's office because of discomfort. Symptoms vary depending on estrogen receptors in the brain. The symptoms usually increase as serum estrogens decline, are variable in frequency and severity, and can persist for several months to years. Dr. Nachtigall pointed out that 80 percent of the symptoms are over within 2 years, and she expressed the view that there are very few women who should not be treated for hot flashes to improve quality-of-life and productivity. She explained that treatment for these symptoms is usually needed for about 2 years and can be gradually withdrawn as the receptors are downregulated.

Dr. Nachtigall described results of a crossover study conducted by Dr. Isaac Schiff and published in the 1980's. Women who were experiencing up to 60 hot flashes a week were given estrogen or placebo. In the estrogen group, the number of hot flashes decreased to zero, assuming the hot flashes were the result of estrogen deficiency, but escalated precipitously when the women were crossed over to placebo. Interestingly, hot flashes in the placebo group decreased by half but never reached zero until the patients in that cohort were crossed



over to estrogen. Dr. Nachtigall theorized that the partial decrease in number of hot flashes in the placebo group could have resulted from self-downregulation by the receptors or endorphin release mediated by the placebo ingestion. She reiterated that estrogen should be withdrawn gradually in view of the findings in the crossover study.

Dr. Nachtigall gave the results of another study by Dr. Schiff that monitored sleep latency, a menopausal event related to receptors in the brain and separate from hot flashes. In the study, patients with sleep latency problems who received drug treatment returned to normal sleep patterns (sleep onset within 10 minutes); in contrast, patients given placebo continued to experience long periods of wakefulness.

Dr. Nachtigall next addressed the management of clinical symptoms from vaginal atrophy, beginning with vaginal dryness. She called attention to a vaginal health index developed by Gloria Bachman, which quantifies characteristics such as elasticity, fluid volume, pH, epithelial integrity, and moisture, and she recommended the use of such an index as being helpful in deciding the severity of a patient's vaginal atrophy. Dr. Nachtigall stated that the use of estrogen effectively manages all symptoms of vaginal atrophy including irritation, burning, pressure, postcoital bleeding, purulent discharge, and dyspareunia. She stated that, unlike other conditions—bone loss for example—vaginal atrophy is totally reversible, and she supported this statement with slides of tissue from vaginal biopsies obtained before and 1 month after treatment with local estrogen. She pointed out that treatment for vaginal atrophy can include local, oral, or transdermal estrogen, any route that transmits estrogen to receptors in the vagina. She called attention to a vaginal ring that was under study at the New York University (NYU) Center as part of the FDA review for approval. The ring contains 2 mg estradiol which is released at 5-10 mcg/24 hrs and lasts for 3 months. Dr. Nachtigall noted that the NYU Center found no evidence of systemic absorption of the estrone sulfate (estradiol). This finding was borne out in statistical information from all other centers that she was able to review. She predicted that when the ring is approved, it will be a viable treatment for post-breast cancer patients because it circumvents the issue of systemic estrogen. She reported that the ring was well received by patients in the NYU Center's study. One finding from the study was that very low doses (5-10 mcg/day) of estrogen are effective. By comparison, dosage for estrogen cream listed in the Physicians' Desk Reference (PDR) is about 2 gms/day.

Dr. Nachtigall concluded that, for vasomotor instability, the physician should plan to treat for 2 years and gradually withdraw treatment. She added that treatment for vaginal atrophy should be initiated at any age and repeated periodically, as needed, because the treatment can be local, very low dose, and intermittent.

Dr. Nachtigall briefly discussed the effect of HRT on sexual function using a slide summarizing the results of a study conducted by Phillip Sorrel at Yale University. The study provided evidence that HRT improves sexual function in all areas--sensitivity, orgasm frequency, orgasm intensity, desire, and behavior--and not just by preventing dyspareunia.

Dr. Nachtigall prefaced her discussion of estrogen and osteoporosis with the reminder that it is the physician who must evaluate the epidemiologic studies and help the patient decide whether to consider long-term HRT for prevention of this disorder. She expressed the view that although prevention is difficult, prevention must be considered in any disease that cannot be cured. In her own experience, patients usually fall into one of three groups: totally committed to hormones, totally against, and undecided. Those who are totally committed to estrogen are started on HRT if there is no contraindication, and then closely monitored. Those who are totally committed to not going on hormone usually are not started on them. The majority of women fall in the undecided category. Dr. Nachtigall advised that if HRT is being considered for its proven long-term benefit in preventing osteoporosis, a bone density scan of the hip and spine is helpful as part of the decision-making process. For patients whose bone density is below the mean (one standard deviation or more), HRT should probably be started and regularly reevaluated. Dr. Nachtigall emphasized the importance of reevaluation because of the probability that new and better estrogens will be developed by pharmaceutical companies in response to the potentially huge market. Patients in the undecided category whose bone density scans show normal density are not started on HRT for osteoporosis prevention, but they should be re-evaluated periodically. Dr. Nachtigall showed pictures of a woman--at age 50 and at age 70 when she was 8 inches shorter to demonstrate how osteoporosis can affect quality-of-life.

Using a slide, Dr. Nachtigall presented the results of a 2-year bone density study in which women were randomized to receive estrogen plus calcium or calcium alone. Bone density decreased in the calcium arm in both the spine and the femur but was preserved and even enhanced over the 2-year period in women on estrogen plus calcium. Dr. Nachtigall concluded that the high-risk woman will continue to lose bone in hip and spine irrespective of the amount of exercise or level of calcium intake. She used the slide of the crossover study introduced earlier by Dr. Stampfer to emphasize the value of estrogen replacement therapy in preventing osteoporotic fractures of the spine and hip.

Dr. Nachtigall summarized the important components of a program to prevent osteoporosis: calcium intake in excess of 1000-1500 mg daily; regular weight-bearing exercise; assessment of clinical risk factors; estrogen supplement in high-risk menopausal women; and identification and removal of factors aggravating bone loss.

Dr. Nachtigall reported that a new drug named alendronate has recently been approved that shows promise as an alternative to estrogen for preventing osteoporosis. Although long-term experience is lacking, alendronate appears to act only on bone, has very few side effects, and increases bone density even after many years of bone loss. Dr. Nachtigall suggested that alendronate could provide a viable alternative for breast cancer survivors at high risk of osteoporosis.

Turning next to cardioprotection, Dr. Nachtigall listed the mechanisms, as introduced earlier by Dr. Stampfer, by which estrogen mediates cardioprotection: increases high-density lipoproteins (HDL) and decreases LDL; exhibits antioxidant properties; and increases coronary blood flow. Because coronary blood flow and antioxidant effect cannot be measured, HDL cholesterol becomes the biological marker. Dr. Nachtigall suggested that a significant decrease in HDL cholesterol levels in menopause is a marker for the patient for the use of estrogen. She pointed out that the 50 years of experience with premarin recommends its use over cholesterol-lowering agents introduced in the market recently, because the new agents have not been thoroughly tested in women.

Dr. Nachtigall presented a slide summarizing coronary occlusion scores by age in postmenopausal estrogen users versus nonusers, which illustrated a benefit for estrogen users in incidence of ischemic heart disease and coronary occlusion. She acknowledged Dr. Stampfer's earlier statement of the need to initiate or encourage lifestyle changes that lower the risk of heart disease, such as exercise and low-fat diets, but she pointed out that the level of compliance is often low. As further evidence of the cardioprotective effect of estrogen, Dr. Nachtigall cited the evidence from Dr. Stampfer's Nurse's Health Study of a decrease in CHD even in estrogen users without risk factors, diabetes, or abnormal cholesterol. Slides summarizing data from other studies demonstrated that progesterone changed the value of estrogen alone by a small amount; that the various ways of administering progestins with estrogen are not significantly different; that low-dose MPA is the best progestogen for total cholesterol lowering; that HDL levels now serve as a marker; and that transdermal estrogen actually decreases triglycerides although the long-range effect is not known.

Turning next to Alzheimer's disease and ERT, Dr. Nachtigall called attention to the results of the Henderson study that was conducted in a retirement community. Women residents on ERT showed better cognitive effect and less Alzheimer's disease than nonusers.

Dr. Nachtigall gave the results of an observational study conducted at the NYU Center. Women were followed for 22 years (a total of 3,271 person-years) to monitor the incidence of breast cancer in that population. Six cancers occurred, which is consistent with the average. However, none of the six patients was on HRT. Dr. Nachtigall concluded that these findings, when added to those in the study reported earlier by Dr. Perlman, provide some comfort in the decisionmaking interactions between physician and patient about long-term HRT.

Dr. Nachtigall stated that her conclusions about breast cancer are similar to those expressed earlier by Dr. Stampfer. Estrogen does not seem to be a carcinogen but does appear to be a growth promotion factor. She noted that until the WHI provides other answers, physicians will have to follow patients carefully to ensure that they do not have an early breast cancer before starting on HRT.

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# THE HRT DECISION-MAKING INTERACTION BETWEEN A WOMAN AND HER HEALTHCARE PROVIDER QUESTIONS AND ANSWERS

Dr. Ralph Yodaiken referred to Dr. Stampfer's list of known risk factors for breast cancer that are related to endogenous estrogens; he suggested that breast feeding and low-fat diet should be added. He noted that many studies suggest a protective effect against breast cancer for women who breast feed exclusively for 3 months or longer and observed that it would be interesting to know if HRT has an impact on these women. He added that, for HRT studies to be complete, the effect of low-fat diets also should be studied in relation to HRT--for example, vegetarian diets that are high in foods containing phytoestrogens. Dr. Stampfer agreed that more information is needed about the long-term effects of breast feeding and about phytoestrogens but noted that he had limited the list to postmenopausal hormones.

Dr. Salmon commented that the WHI is a very important study but long overdue in light of the wide-scale introduction of medication into millions of women without adequate scientific and data-based treatment information. He expressed the view that there are alternative ways of dealing with the major reasons that HRT has been prescribed, mainly cardiovascular disease and osteoporosis. He suggested that the paradigm of HRT is now a serious issue for long-term use.

Dr. Dickersin requested that the term "normal woman" not be used to refer to a woman without breast cancer. She suggested that other words can be chosen. She asked Dr. Rossouw how investigators in the WHI planned to continue to gather information about HRT and breast cancer if the trial is stopped early because of a confirmed beneficial effect for cardiovascular disease. Dr. Rossouw replied that a more robust estimate of HRT will be obtained from combining the estrogen alone and estrogen plus progesterone arms and comparing them to the placebo group because that can be done within the trial period. This will be done if similar effects are found for the combination and single therapies. The alternative strategy is to do a followup study to achieve sufficient power. The assumption in that event would be that some women will continue treatment because they like it and that there will be some carry-over effect.

Dr. Rimer asked Dr. Perlman if the investigations leading to the choice of Megace® as the progestogen of choice considered the quality-of-life impact of weight gain that is often associated with Megace®. Dr. Perlman replied that one of the purposes of the study would be to reduce the dosage of Megace®.

Dr. Rimer asked Dr. Perlman if there were enough breast cancer survivors in his analysis to do a subgroup analysis by tumor markers. Dr. Perlman replied that there were not.

Ms. Mayer referred to the summary of abstracts that had been distributed and noted that her intent was to provide a snapshot of ongoing research activities and the award mechanisms. She identified the topic "Decision-making for Women Facing the Issue of HRT" as an area of interest, noting only one study in that area. She expressed the hope that one outcome of the symposium would be some type of commentary written for the Journal of the National Cancer Institute to stimulate interest in some of the areas still needing research. In concluding the symposium, she asked the Board to join her in thanking the panelists for the morning's presentations.

Dr. Rimer announced that the next topic on the agenda, the tamoxifen trial update, was planned in response to requests from Board members. She introduced Dr. Peter Greenwald to present background information on the tamoxifen trial.

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## TAMOXIFEN TRIAL UPDATE

Dr. Greenwald reminded the Board that the Breast Cancer Prevention Trial (BCPT) with tamoxifen had been planned and developed by the NSABP clinical cooperative group as part of the CCOP. He stated that investigators in the NSABP and colleagues in the NCI led by Dr. Leslie Ford recently have carried the study through a difficult and unfortunate period for the clinical trials, and he introduced Dr. Ford to proceed with the update. <>Dr. Ford expressed pleasure that the BCPT is thriving, and she credited the actions of the Board over the previous 2 years for the success, particularly the Board resolution approved in June 1994 which stated that "the National Cancer Advisory Board considers the BCPT to be one of the most important trials sponsored by the National Cancer Institute." She acknowledged the invaluable assistance from her staff, Dr. Karen Johnson, Ms. Rose Mary Padberg, and Ms. Jennifer Flach, and the work of the NSABP staff led by Dr. Barry Wickerham, Dr. Walter Cronin, and Dr. Maury Salides.

Dr. Ford presented a brief overview of the trial. The BCPT will involve 16,000 women at increased risk for developing breast cancer. This risk is determined using the Gail model that is based on several factors--age at menarche, age at menopause, family history of breast cancer, and history of breast biopsies and their pathology. Women will be randomized to receive tamoxifen (20 mg/day) or placebo for a 5-year period. The primary study endpoints are invasive breast cancer incidence and mortality, bone fractures, cancers of all causes, and all causes of mortality. A unique feature of BCPT is that quality-of-life data are collected routinely. Dr. Ford reported that the baseline quality-of-life results have already been published, and the quality-of-life analyses will be integrated into the overall analysis of the potential benefits or risks of tamoxifen. In addition, detailed companion studies will look at endometrial changes in the presence of tamoxifen or placebo, bone mineral density in pre- and postmenopausal women on both arms, and new developments in the area of genetics.

Dr. Ford reported on the current status of the study. Randomization began in June 1992 and was temporarily interrupted in April 1994 for a 6-month period because of administrative problems. To date, 11,875 women are enrolled in 284 sites throughout the United States and Canada. Age distribution of the study population is as close to original projections as possible with 40 percent under age 50, 30 percent between ages 50 and 60, and 30 percent over age 60. Almost 80 percent of the individuals in the study had risk profiles that included at least one first degree relative with breast cancer, and 20 percent had two or more.

Dr. Ford noted that, in terms of breast pathology, BCPT has the largest number of women with lobular carcinoma in situ (LCIS) and with diagnosed atypical hyperplasia that have ever been followed in a carefully controlled randomized setting. Dr. Ford showed a slide depicting the actual risks of the population of women who have chosen to be randomized into the study, and she pointed out that almost all women have double the minimum increased risk (SEER data on average annual incidence rates were used as a baseline). Dr. Ford explained that the women were able to make informed decisions about entering the study because of the information they receive prior to agreeing to be randomized. Risk profiles based on the Gail model were generated for each of the women from information provided by the women. Also included with this individualized risk assessment is information about potential benefits and risks of participating in the BCPT. Dr. Ford pointed out that the profiles for postmenopausal women differ from those of younger women because of the increased risk for endometrial cancers and blood clots. These women are given enough information to be able to see the balance between prevention of breast cancer and a potential risk of endometrial cancer or blood clots.

Using a slide, Dr. Ford reviewed the recently amended analysis summarizing the actual risks and benefits of the 11,000 women in the BCPT. This risk-benefit analysis is part of the most current version of the protocol, and it summarizes the number of predicted events--both potential benefits and potential detrimental effects--in the areas of breast cancer, CHD, endometrial cancer, liver cancer, and pulmonary embolisms to produce a net benefit estimate. Dr. Ford pointed out that the estimated bases for the calculations--30 percent reduction in breast cancer and 20 percent reduction in CHD--are conservative compared with findings in other clinical trials. In every case, the analysis shows a net benefit. The analysis is also based on a threefold increase in endometrial cancer which, according to Dr. Ford, is also conservative, because it does not account for the high rate of hysterectomies in this population, and it does not include any benefit derived from endometrial monitoring. In that regard, Dr. Ford noted that a requirement for prestudy endometrial sampling was

introduced in October 1994 to supplement the original requirement for an annual gynecologic examination. The study is providing funds for annual endometrial sampling for women entering the study before October 1994, and there are plans for a substudy looking at the value of ultrasound versus endometrial sampling as a means for following uterine changes in a group of women on tamoxifen or placebo.

Dr. Ford presented unpublished data from a study initiated 2 years previously by DCPC in four sites in the SEER network. Investigators, under the leadership of Leslie Bernstein at the University of Southern California, are looking at all breast cancer patients from the SEER registry who were subsequently diagnosed with endometrial cancer. The controls are breast cancer patients who did not develop a subsequent endometrial cancer. The study will attempt to determine the risk of endometrial cancer in breast cancer patients who used tamoxifen versus those who did not, as well as to understand factors that may contribute to those outcomes. Investigators will obtain a detailed history of dose and length of exposure to tamoxifen as well as a detailed history of prior hormone replacement in all forms (OCs, estrogen, estrogen plus progestin). Dr. Ford reported that preliminary data from the study seem to indicate that the excess risk of endometrial cancer in breast cancer patients who have taken tamoxifen is related to prior exposure to hormone replacement.

Dr. Ford reported on the expansion of the BCPT to take into account genetic evaluation. She reminded the Board that this study has already enrolled women who fall into several exceptional risk categories, including a large group with LCIS and the large percentage with one or more first degree relatives with breast cancer. Currently, the study is expanding the eligibility criteria for enrollment to include women over age 35 if they have been commercially tested and found to have a BRCA1 variant. In line with this new direction, BCPT investigators are about to begin work with Drs. Mary Claire King and Wylie Burke at the Fred Hutchinson Cancer Center that will build on preliminary investigations conducted as part of the B-14 study of tamoxifen in node negative breast cancer patients. The role of Drs. King and Burke will be to conduct a case-control study of women who have developed a contralateral breast cancer, with controls who are either matched cases or cases from the general population of B-14 (the latter has not yet been decided). The purpose of the study is to see if differences exist in BRCA1 variants between those who do and those who do not develop contralateral breast cancer. Preliminary work will also be done to discover what effect, if any, tamoxifen has had on the development of contralateral breast cancer. Follow-on work is planned in the BCPT to look for differences in first breast cancer occurrences between BRCA-variant and BRCA-normal participants. Part of the BCPT plan is analysis of data to see whether tamoxifen has a differential effect in women who have a known genetic predisposition to developing breast cancer.

Dr. Ford noted that the most frequent questions about BCPT relate to minority recruitment efforts and compliance issues. She addressed the first issue with the following information. BCPT performed 77,000 risk assessments on potential enrollees, 92 percent from white women and 8 percent from women of color. Of these, 95 percent of the white women and 5 percent of the women of color were eligible for BCPT participation. At the present time, the figures for white women and women of color who are enrolled and randomized are 93 percent and 3 percent, respectively. Dr. Ford pointed out that although the minority accrual figure is low, BCPT minority recruitment has seen a substantial increase since the problem was recognized at the end of the first year of the study, increasing from 9 percent in 1993 to between 12 percent and 15 percent in 1995, and 5 to 6 percent of the women now being randomized are women of color. Another finding is that 63 percent of the white women who submit risk assessment forms are eligible for enrollment compared with 36 percent of the women of color. Another loss to minority recruitment numbers is the fact that 25 percent of white women assessed as eligible for study participation agree to be randomized compared with only 17 percent of the women of color. Dr. Ford concluded that these figures indicate that women of color are interested and can be reached but there is much work to be done in the whole field of prevention trials. She stated that it has been possible to identify problems in the area of prevention and DCPC and its investigators are working on them, but some problems may be beyond their control.

Turning next to the issue of compliance, Dr. Ford affirmed that the events surrounding the April 1994 interruption in the accrual process did affect compliance rates, but the noncompliance rate of 30 percent must be considered in the context of the study's protocol development. She explained that the original sample size calculations and projections were based on 10 percent per year noncompliance rate. At the end of 36 months of

followup, 27 percent of the original population would be expected to have gone off the study for nonprotocol-specific reasons. Dr. Ford stated that the observed figure is 32 percent. She presented a summary of expected and observed quarterly compliance rates, which revealed quarters with higher than expected noncompliance. She noted that these peaks coincided with the congressional hearings and an informed consent change, and she indicated that the rate at 36 months is less than 1 percent, not 2.5 percent as projected. Dr. Ford--expressed the view that BCPT now has a population committed to staying on the study until it is completed.

Next, Dr. Ford reviewed recent recruitment and compliance activities. A participant advisory board, which has been meeting for 2 years, has made a video of a panel discussion, in which advisory board members were the panelists, featured at the most recent NSABP meeting. A participant recruitment workshop has been scheduled to interest participants, nominated by coordinators throughout the country, in expanding their roles in BCPT to assist with recruitment and compliance activities. A participant newsletter is being circulated as part of the "each one reach one" campaign. Relationships with the Komen Foundation have resulted in several outreach initiatives: Dr. Ford spoke to state chapter members and Race for the Cure coordinators at the annual affiliates meeting; BCPT risk assessment forms are being placed in the packets that will be distributed to the more than 300,000 women expected to participate in the 1996 race; and foundation chapters in areas where BCPT has recruitment sites have offered assistance in recruitment and compliance activities. DCPC staff are working with the NCI Office of Cancer Communications outreach coordinators on projects to increase the accrual rate. A pilot project has been started in five BCPT sites with the possibility of expansion to other sites; part-time community outreach coordinators will be hired to assist in the recruitment of women of color. New centers and subcenters are being evaluated as potential BCPT study sites.

Dr. Ford concluded her presentation with a showing of the video of the participant advisory board panel discussion.

Dr. Rimer thanked Dr. Ford for addressing questions that probably would have been asked. She commended the attempts to reach minority member and noted that the BCPT's experience in this regard would be instructive to others planning recruitment trials. She called attention to the copy of the Board's 1994 resolution and suggested that the Board may find it useful to reevaluate its position during the discussion period.

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## TAMOXIFEN TRIAL UPDATE QUESTIONS AND ANSWERS

Ms. Mayer asked if, in the interest of increasing minority recruitment, there were plans to oversample for women of color in the recruitment time remaining or to work toward closing the gap between the number of women of color found to be eligible for the BCPT and the number who actually enter. Dr. Ford replied that the job of the outreach coordinators will be to encourage eligible women to choose to participate. She noted, however, that oversampling is a complicated issue and would require the involvement of the data monitoring and steering committees and a number of boards.

Ms. Zora Brown asked if BCPT coordinators had identified either the common reasons why enrolled and randomized women leave the study or the barriers preventing them from continuing. Dr. Ford replied that some women have left because of intolerable hot flashes associated with tamoxifen and the inability to relieve them with any kind of hormone treatment while on the study. Others have left because of the fear that they have a 50 percent chance of being randomized to the tamoxifen arm and are subjecting themselves to endometrial cancer risk or endometrial biopsies. Some women are compliant for 2 years or more before leaving. Dr. Ford noted that BCPT investigators and the DCPC staff are working to overcome all of these stumbling blocks. Re-recruitment is always attempted and these efforts have met with some success.

Dr. Rossouw commented that minority recruitment is an issue of concern in the WHI also, and he commended Dr. Ford and the BCPT investigators for persevering in the face of considerable adversity. He stated that WHI now has considerable experience with recruiting minority women and better than average success; 19.2 percent

of the randomized participants are women of color, and the goal of 20 percent is expected to be reached. He attributed this success to the structural differences in WHI compared with other studies in that 10 percent of the 40 WHI sites are designated minority centers, and they contractually must recruit minorities. At other WHI sites, between 8 percent and 12 percent of the participants are women of color. Dr. Rossouw stated that the plans are to close recruitment for nonminority women in those 10 centers as soon as their goals are reached so they can concentrate on minorities. He described differences in the screening practices between BCPT and WHI and suggested that BCPT may be experiencing difficulty because of the particular risk factor algorithm. He noted that WHI investigators are focusing strongly on the issue of higher dropout rates in minority women during the initial screening stage. He suggested the possibility of reconfiguring some of the BCPT centers to make them more sensitive to the goal of increasing minority recruitment.

Dr. Ford responded that BCPT centers include minority-based CCOPs, which recruit almost 50 percent of their new cancer patients in minority groups into treatment clinical trials. These centers are having a difficult time randomizing to BCPT and to the prostate prevention trial. Moreover, BCPT personnel have been in close contact with WHI minority recruitment sites and the minority recruitment committee. She agreed with Dr. Rossouw that having a screening and eligibility factor that is causing the loss of a large number of interested women is an issue.

Dr. Dickersin asked about the truth in rumors that four data monitoring committee meetings had been held in the previous 6 months. Dr. Ford replied that a regularly scheduled meeting was held in September 1995 and another is scheduled for April 1; in addition, an ad hoc meeting was held to discuss the monitoring of multiple endpoints. She added that the data monitoring committee receives all new information.

Dr. Dickersin asked if the gynecological monitoring for endometrial changes in BCPT differed from that in other NCI trials. Dr. Ford responded that the difference is that BCPT pays for the biopsies because a precise assessment of endometrial changes and of all risks is needed for a prevention study before a woman without a diagnosed disease can be asked to take a medication. The same practice standards are recommended in the treatment setting, but the NCI usually does not provide funds for what is considered routine management.

Dr. Salmon commended Dr. Ford for carrying the study through hard times, and he expressed satisfaction that the Board resolution helped get the study back on track. He observed that there was a tendency for younger women to enroll in the BCPT as opposed to what was envisioned originally, and he asked if the mean had shifted to an older age. Dr. Ford stated that, to the contrary, the BCPT population had never encompassed the younger age group. She explained that sample size calculations had been based on a certain risk level and three different scenarios of age distribution and the BCPT population mirrors the middle-age group as envisioned in the original estimates (up to 40 percent under age 50 and 60 percent postmenopausal). Dr. Salmon asked if the middle-age group was defined by age or risks. Dr. Ford replied that the risks were standardized to be at least the risks of the average 60-year-old woman based on age, which factored in cardiovascular risk. Dr. Salmon asked whether the NHLBI considered the BCPT population to be not old enough. Dr. Ford explained that subsequent to the NCI's decision to proceed based on the original age scenarios, NHLBI changed the parameters. She added that the NCI has not changed anything in the trial and considers cardiovascular endpoints to be an important factor in the risk-benefit calculations. These endpoints are being monitored, and the protocol has not been changed relative to EKGs.

Dr. Day pointed out that the identification of observable genetic risk factors constitutes a big change. He asked that the next Board agenda include a review of NCI trials from that perspective because of the valuable new information that is available. He asked for information about the planned review of NCI clinical trials. Dr. Klausner explained that a special working group is examining all aspects of NCI clinical trials including technology issues (molecular diagnosis and detection), and he agreed that these issues could be addressed at the May meeting. Dr. Day expressed the view that investigators in NCI clinical trials would not be proceeding as judiciously as they should without that understanding. He acknowledged that there are issues about this or any study design involving genotyping that raise questions about the interpretation of the results, and noted that the BCPT has the added complexity of evaluating the side effects of the study drug. He emphasized the importance of being able to assess risk of breast cancer more definitively. Dr. Rimer agreed to work with Dr. Day, Dr.

Alfred Knudson, Dr. Ford, and others to frame the discussion on these issues before the May meeting.

Dr. Paul Calabresi pointed out that one of the concerns of the BCPT is the increased risk of uterine cancer, and he asked Dr. Ford to summarize what is known about the use of progestational agents with tamoxifen. Dr. Ford referred to the answers provided by Dr. Perlman in his presentation, noting that very little is known about progestational agents and breast cancer. She reported that the NCI is sponsoring a few studies in the clinical cooperative groups to evaluate whether adding short-term progestational agents to the tamoxifen for women being treated for breast cancer will alleviate the incidence of endometrial hyperplasias. There are no plans to study this effect in the context of this tamoxifen study because of the need for focusing exclusively on the effects of tamoxifen on the breast and uterus to produce more conclusive evidence on which to base advice to women. She predicted, for example, that clinical practice related to obtaining endometrial biopsy samples before initiating tamoxifen treatment following breast cancer surgery will change if the BCPT data on prior use of hormones hold up. She pointed out the value of having one cohort of women in BCPT who are certified as being without endometrial hyperplasia before they are randomized.

Dr. Pelayo Correa asked about the early reports that the endometrial cancer related to prior use of tamoxifen differed from the carcinomas related to the use of estrogen. Dr. Ford replied that this was merely early anecdotal information. Published case-control studies have shown the same type of case distribution in breast cancer patients receiving tamoxifen who get a subsequent endometrial cancer as seen in estrogen users. The same distribution of pathologies was confirmed in the unpublished study by Leslie Bernstein and in studies conducted at Memorial Sloan-Kettering Institute.

Dr. Chan referred to Dr. Day's discussion about genetic identification and suggested the need for the Board to consider issues related to protecting the confidentiality of such information.

Dr. Schein observed that the beta-carotene study has provided investigators with a new perspective on the potential risks associated with a large-scale prevention trial. He expressed the need to ensure that the BCPT is being carefully monitored for adverse experiences and that these are reported immediately to the Board and others. Dr. Ford replied that the data monitoring committee meets at least twice a year to evaluate unblinded data. The committee has well-thought-out plans for multiple endpoint monitoring and rules to follow if one endpoint seems to be appearing before others. The committee chair, Dr. Ted Colton, and others on the committee have much experience in this area of investigation and keep the steering committee informed of committee deliberations and findings.

Dr. Rimer asked Dr. Ford to comment on the recent International Agency for Research on Cancer (IARC) report. Dr. Ford replied that the report in question focused only on previously published data that showed an increased risk of endometrial cancer in tamoxifen versus placebo studies. This information has been known since 1991, was included in the original protocol design and consent form for BCPT, and continues to be part of the risk assessment. Dr. Ford pointed out that the report did not include the unpublished data she had presented earlier, and might be considered by some as a premature categorization. She noted that the first IARC statement reported that tamoxifen has been clearly shown to reduce contralateral breast cancer, and that there is no evidence of an increase for any other cancers.

Dr. Dickersin asked whether one can be sure the results of a 5-year study of the protective effect of tamoxifen in high-risk women can be extrapolated to show protection for women with genetic predisposition who are high risk for a lifetime, given the results of the NSABP B-14 study. Dr. Ford stated that is not known. She referred to the 5- and 10-year curves from the B-14 study and noted that the rate did not increase in the women who stopped the drug after 5 years. She acknowledged that it is not known whether tamoxifen must be taken for life to prevent breast cancer. Plans are to stop BCPT at 5 years and then monitor the women for life.

Dr. Rimer commended the diligence with which Dr. Ford and her staff have been reporting to the Board.

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## SUBCOMMITTEE REPORTS



Report on Ad Hoc Subcommittee to Evaluate the National Cancer Program

Report on Basic and Environmental Cancer Research Subcommittee

Report on Planning and Budget Subcommittee

Report on Cancer Centers Subcommittee

Report on Information and Cancer Control Subcommittee

Report on Clinical Investigations Subcommittee

Report on Special Priorities Subcommittee

Report on the Meeting of the Advisory Committee to the Director of the National Institutes of Health

Report on Activities and Agenda Subcommittee

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## **REPORT ON AD HOC SUBCOMMITTEE TO EVALUATE THE NATIONAL CANCER PROGRAM**

Dr. Day reported that the Subcommittee discussed activities of the interagency working group, which looked at the feasibility of creating an inventory of cancer research across Federal agencies. The working group is evaluating the utility of a newly developed database called RaDiUS. A pilot test was conducted but final information was not available. The Subcommittee also heard a report from Dr. Freeman, who spoke to the concept of forming an organization or council similar to the Institute of Medicine as an additional means of addressing the National Cancer Program. Dr. Day noted that this issue is ongoing and will involve the Board at various stages. A third report was heard from Dr. Edward Sondik, Associate Director for Strategic Planning, the NCI, who briefly described the makeup, areas of responsibility, and means of reporting by the NCI working groups being formed to review major programs within the Institute.

Dr. Day summarized the issues discussed by the Subcommittee: (1) how much to press the coordination of all of the cancer activities as called for under the National Cancer Act; and (2) the possibility of querying members and ex officio members of the Board and liaison representatives in an attempt to identify an easier way to derive information about the extent of cancer research throughout the Government. He noted that the committee will continue followup on these issues and that during this meeting the Environmental Subcommittee would be reporting their results of an environmental cancer research inventory.

The Board passed a motion to approve the Subcommittee minutes.

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## **REPORT ON BASIC AND ENVIRONMENTAL CANCER RESEARCH SUBCOMMITTEE**

Dr. Becker reported that the Subcommittee has been working to inventory research on environmental cancer across Federal agencies, including the funding levels. He thanked Dr. Susan Sieber and acknowledged the cooperation from others, including Dr. Hugh McKinnon of the Environmental Protection Agency (EPA), for their efforts in this regard. One area of interest was funding devoted to research defined broadly, which excluded monies devoted to regulation and some prevention studies. Dr. Becker noted that the Occupational Safety and Health Administration (OSHA), which devotes much money to occupational cancer, will be excluded

from the chart in the written minutes because the vast bulk of its \$92M budget was spent on enforcement and \$3.2M was spent on regulatory development.

Dr. Becker stated that Board members would receive copies of a booklet prepared by Dr. Sieber entitled "The Investment in Research into Environmental Carcinogenesis," which contains much information that will be helpful in responding to critics. He noted that the figures represent the Subcommittee's best efforts, given the problems with definitions--for example, whether herbicides and pesticides were part of occupation, air pollution, or general environment--and the difficulty in obtaining information from some agencies.

Dr. Becker stated that the Subcommittee had another mission that paralleled the discussions in the meeting. The question was raised as to why subcommittee meetings were held and what the role of NCAB subcommittees was to be in the future. As a result of the discussion, the Subcommittee recommended (1) that its future activities should be deferred until decisions are reached concerning the future goals of the subcommittees; (2) that the goals of subcommittee activities should be determined in support of major areas of interest and actions in the bypass budget and not in response to NCAB membership; (3) that if the committee is reactivated, it should be used as a means of coordinating some substantive activities pursued by more than one agency; (4) that to delineate the best role for NCAB subcommittees, the goals, missions, and durations of activities of all extra NCAB committees should be clearly defined; and (5) that a substantial portion of an NCAB meeting, perhaps 2 to 3 hours, should be devoted to goals, policies, and future functions of the NCAB.

Dr. Rimer stated that she supported the recommendations. Her observation of subcommittee meetings when she became chair were that some were working very well and others were searching for a mission. On the basis of these observations and because the mission of the NCI has changed in the past year, Dr. Rimer concurred that it is important to take time to solve the question of what subcommittees are needed, without being constrained by the committees that already exist. She announced that she and Dr. Kalt are planning a retreat that will include, if possible, NCI Executive Committee members, other appropriate NCI staff, and representatives from the Board of Scientific Advisors. The purpose of the retreat would be to consider the question of goals in general and of subcommittees as well. Dr. Becker endorsed this plan and suggested for consideration at the retreat that subcommittees should be evaluated every year to see if they are fulfilling a need and acting in support of the NCAB and the NCI.

Dr. Sigal asked Dr. Becker what action the NCAB could take, now that all the data on environmental carcinogenesis have been assembled. Dr. Becker recommended postponing any action until all other external committees have completed their review of the entire NCI program.

The Board passed a motion to approve the Subcommittee minutes.

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## REPORT ON PLANNING AND BUDGET SUBCOMMITTEE

Dr. Sigal reported that the Subcommittee unanimously endorsed the concept of the Howard Temin Extended Support Award with great enthusiasm. She referred to copies of the bypass budget that had been circulated to the Board and asked that all comments be submitted to Ms. Cherie Nichols, Executive Secretary, by the Monday following the NCAB meeting, with copies faxed to her. She asked also that Board members review the list of organizations appended to the written minutes and add to it as appropriate. The Subcommittee plans to send copies of the next draft of the bypass budget to these organizations for review. Dr. Rimer thanked Dr. Sigal and the Subcommittee for their efforts in this regard.

The Board passed a motion to approve the Subcommittee minutes.

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## REPORT ON CANCER CENTERS SUBCOMMITTEE

Dr. Day reported that the Cancer Centers Working Group expects to have completed its review and report to the Board of Scientific Advisors and Dr. Klausner by summer. Dr. Margaret Holmes was queried about the Cancer Centers budget and provided the information as recommended levels. A total of 16 planning grants have been awarded, including 3 new grants funded in fiscal year 1995. However, the grant periods for the original 13 have expired and these grants are currently in an unfunded continuation year. Dr. Day noted that some of the 13 have applied in the current year to become Cancer Centers. Two new Cancer Centers--Jefferson and Vanderbilt--were added in fiscal year 1995 but did not have planning grants. The Subcommittee also discussed the issues of managed care and clinical research, which continues to be a major concern for Cancer Centers. DR. Rimer thanked the NCI staff who are working with the Subcommittee on some of these issues of major interest to the Board.

The Board passed a motion to approve the Subcommittee minutes.

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## REPORT ON INFORMATION AND CANCER CONTROL SUBCOMMITTEE

Ms. Malek reported that the Subcommittee continues to plan for a 1-day conference on Women and Tobacco to be held on Capital Hill in June. The Board will be informed of the date and list of speakers as soon as plans are final. Dr. Rimer thanked Ms. Malek for her work on the Subcommittee and especially for her work in planning the conference. There was no Subcommittee meeting and therefore no report to approve.

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## REPORT ON CLINICAL INVESTIGATIONS SUBCOMMITTEE

Although this Subcommittee did not meet, Dr. Rimer pointed out that the biotechnology minisymposium presented earlier in the meeting was an outgrowth of this Subcommittee's activities. Dr. Schein observed that Dr. Klausner had preempted the Subcommittee will monitor the progress of the clinical research program and support it in every way possible. Issues raised for discussion in the minisymposium will be agenda items for Subcommittee discussion and possible items for formal attention by the Board. There was no Subcommittee report.

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## REPORT ON SPECIAL PRIORITIES SUBCOMMITTEE

Dr. Rimer acknowledged the work of Ms. Brown, Ms. Schneider, and Dr. Paulette Gray in helping to sponsor a conference and develop the Request for Application (RFA) concept for R13 grants for regional conferences on the recruitment and retention of minority participants in clinical trials research. Ms. Brown acknowledged and praised the efforts of Ms. Schneider and Dr. Gray in organizing the national conference, which was held in January 1996. The conference was an outgrowth of Board discussions of problems related to recruiting and retaining minorities in clinical trials. The RFA for R13 grants was developed as a result of conference deliberations. The objective is to provide support for the regional conferences to share current information and strategies that will aid the clinical investigators. Another objective of the conferences was to define additional research needs and to promote collaborations among cancer clinical investigators that will further the representation of minorities in their studies.

Ms. Brown reported that a conference call was held during the week before the NCAB meeting to expedite discussion and voting on the RFA for regional conferences. The Subcommittee endorsed the emphasis on prevention trials in the Goals and Major Objectives section; recommended that inclusion of older Americans in proportion to the incidence of cancer in that population should be encouraged but not required; encouraged partnerships with private sector and public organizations that can reach minority communities through

education and outreach efforts before clinical trials are initiated; emphasized circulating the national conference report to the regional conferences; suggested that proportionality should be a minimum requirement because oversampling of minorities may be necessary to do a valid analysis of minority differences; and suggested that the RFA state that prevention trials have too few participants.

Ms. Brown commended the efforts of Ms. Schneider and Dr. Gray in developing the RFA so soon after concept proposal, noting that the grant could be published in the NIH Guide and Grants and Contracts as early as March with first grants awarded by summer. Dr. Goldson recognized the efforts of the NCI staff in this regard and pointed out that the rapid turnaround from concept to RFA showed how effectively the subcommittees can act when time and effort are focused on a specific product.

Dr. Rimer called attention to the copies of the concept that had been distributed and asked for a motion for approval. The Board passed a motion to approve the concept as presented.

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## REPORT ON THE MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR OF THE NIH

Dr. Rimer thanked Dr. Correa for representing the Board at the recent meeting of the advisory committee. Dr. Correa called attention to the material that had been distributed by Dr. Pizzo explaining how the committee operates. He pointed out that the current meetings represent the organizational phase of the review, and he commended that seriousness with which this subject is being addressed at both the NCI and NIH levels, as well as the abilities of the subcommittee leaders in this effort.

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## REPORT ON ACTIVITIES AND AGENDA SUBCOMMITTEE

Dr. Rimer stated that the Subcommittee conferred by telephone in lieu of traveling to Chicago in January. One topic for discussion was the NCAB subcommittees, their diversity, and the extent of their effectiveness. Another focused on the need for periodic updating on progress in meeting the goals established in the Bishop-Calabresi report and on progress of the NIH review committees. Dr. Rimer announced that the May NCAB meeting agenda will devote considerable time to updates on the review process. Two topics--genetic risk and gene therapy--were suggested for future meeting discussions.

Dr. Rimer announced that as an outgrowth of the analysis of NIH councils, Dr. Varmus is instituting a committee of NIH Council representatives. A meeting of the committee will be held on March 14, which Dr. Rimer and Dr. Sigal will attend.

Turning next to the issue of planning for the Board retreat, Dr. Rimer asked outgoing members to indicate if they would be willing to attend the retreat and to submit possible dates they would be available.

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## CONTINUING AND NEW BUSINESS SESSION II

Dr. Rimer gave the Board an opportunity to bring new business items to the floor.

Dr. Sigal emphasized the importance attached to the issue of managed care and the survival of Cancer Centers by the Subcommittee on Cancer Centers, and she suggested this as a future agenda item, particularly if it can be approached from another perspective. Dr. Rimer recommended that the Subcommittee continue to address this

issue, and she ascertained that an update on deliberations with managed care organizations might be possible. Dr. Klausner characterized the negotiations as preliminary and cautioned against expecting much information at this time. Dr. Becker expressed the view, based on conversations with Cancer Center directors, that financial problems facing Cancer Centers are greater than the support of clinical research, and even the successful conclusion of negotiations with managed care organizations will not assuage the impact of declining income in the Centers' overall budgets. He praised the efforts of Dr. Rimer and Dr. Wittes in this regard but cautioned against thinking that there are easy solutions. Dr. Day suggested that, because there is concern also for academic health centers and institutions located in the intercity, it might be of interest to frame the discussions in the larger context. He suggested that it might be of interest to invite others in the DHHS who are concerned as well.

Dr. Salmon agreed with Dr. Becker's comments and suggested the need for a comprehensive analysis of the impact of changes in the health care environment on Cancer Centers, based on quantitative information from a large number of Cancer Center directors. He suggested that possibility of gathering information at the spring workshop of directors of Cancer Centers, if the agenda permits. Dr. Rimer raised the possibility of asking Dr. Wittes to conduct a survey.

Dr. Boxer emphasized that the effort of managed care on academic health centers is a critical issue that should be addressed. However, the 40M uninsured without access to any care will have a much greater impact on cancer in general.

Dr. Becker pointed out that the impact of smoking on cancer incidence is one problem on which all agree, and noted that one problem in addressing the issue is that smoking has always been dealt with as a colossal problem. He suggested smoking as a future agenda item but with a focus on dealing with highly specific problems in smoking--behavior modifications, for example. He suggested that the topic could be approached much as the environmental carcinogenesis study was handled by the Subcommittee, by surveying agencies to determine funding devoted toward research into the problem of smoking and then attacking specific areas in a substantive way. Dr. Rimer agreed that smoking research is an important issue and that information about actual spending is needed. Shee pointed out that the NCI cancer control and prevention review will be conducted in coming months and the allocation of resources to this area should be an integral part of that review.

Ms. Brown suggested lymphedema and its association with breast cancer treatment as a future agenda item. Dr. Rimer agreed that it is an important quality-of-life issue.

Dr. Rimer asked for final comments from Dr. Kalt, Director, Division of Extramural Activities (DEA). Dr. Kalt reported that preparations for the grant application review at the May NCAB meeting will be somewhat off schedule because the meetings of the Division of Research Grants (DRG) study section and the DEA initial review group were delayed by the furlough. He noted, therefore, that Board members will receive a number of summary statements very close to the meeting date, but that the May meeting will take care of applications submitted and reviewed late in the cycle. He pointed out that the list of delayed reviews can be accessed on the NIH HomePage, that nothing has been missed, and that applicants have usually been carried administratively and without penalties. Dr. Rimer commended the work of the NCI staff in keeping to the grant review schedule in spite of the furlough and snow delays.

Dr. Kalt reported that the NCI is experimenting with a new approach to Phase I and Phase II Small Business Innovation Research (SBIR) awards--R43 and R44, respectively. Small businesses may submit Phase I and Phase II applications for review at the same time. If the applications receive a high enough priority score, they will be in position for receiving continuous funding through both phases of research. The current system requires successful completion of Phase I before application could be made for a Phase II award, creating a disturbing interruption of funding for small businesses. Dr. Kalt pointed out that there is some uncertainty as to how the DRG will handle the review, because Phase II applications will have much less documentation. He added that the Board would receive the first of these SBIRs for review at the May meeting. Dr. Kalt noted that grantees will not receive both awards at the same time; the grantees must demonstrate adequate progress as determined by administrative programmatic review of the Phase I results.

Dr. Kalt described a second innovative extramural paradigm being initiated by the NCI. He reminded Board members of the existence of the NIH Shannon award, which pays \$100,000 per year for 2 years to investigators with innovative ideas whose applications received scores close to the payline. The NCI has received permission to make its own Shannon awards. The NCI portfolio of applications will be reviewed after each of the three grant rounds for applications that have the potential to receive NCI Shannon awards. There may be overlap with the AER in that some applications that the NCI cannot fund under that principle may be offered an immediate Shannon award. This innovation has the potential to add another 30 awards to the 1996 total and represents another means for getting awards into the hands of investigators in or close to the same cycle of the application. Dr. Kalt pointed out that investigators will still have an opportunity to submit an amendment and complete for a follow-on R01. If they are successful, the funding remaining in the Shannon award will be deducted from the new award. Board members will see the summary statements as regular R01s and R29s, because Shannon awards are made after the grant rounds have been completed. Board members may also suggest grants of interest that are outside the payline for Shannon award consideration by the Executive Committee.

Dr. Rimer thanked Dr. Kalt and introduced Dr. Livingston to discuss the Extramural Board of Scientific Advisors (BSA).

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## **BOARD OF EXTRAMURAL SCIENTIFIC ADVISORS STATUS REPORT**

Dr. Livingston likened the current development of NCI programs to a renaissance from which shapes of considerable appeal and extraordinary color are emerging. He expressed the hope that, in coming years, he would be able to give a sense of the new configuration as he reports on behalf of the BSA. Among other matters, the BSA will report on relevant matters under discussion in the Executive Committee, which is the segment of the NCI that deals with policy; in the operating divisions; and among investigators in the extramural community. The BSA will meet with extramural researchers at national cancer research meetings of various types each year as a means of bringing outside scientific opinion on NCI operations to NCI leadership. He reported that the names of the 32-member BSA will be announced publicly as soon as the NIH nomination and confirmation process is concluded. Dr. Livingston described the BSA members as a geographically and ethnically diverse group of experts in their fields, most with prior oversight or leadership experience and specifically chosen to represent each of the major extramural research constituencies of the Institute. The BSA also includes leading members of the consumer community. For operating purposes, the BSA will be divided into two subcommittees; one devoted to clinical research, prevention, cancer control, and early diagnosis; the other to cancer biology, epidemiology, and genetics. The subcommittees will meet in separate sessions during each BSA meeting to gather information and then deliberate as one Board. It is these deliberations that all of the formal and substantive decision making will take place.

Dr. Livingston reported on the status of the reviews that the BSA is undertaking. The committee reviewing the NCI Cancer Centers Program, with Dr. Joseph Simone as Chair and Dr. Gray as Executive Secretary, expects to submit a written report by summer to the Director, the BSA, and the NCAB. A review of the Clinical Trials Program is to be initiated soon under the leadership of Dr. James Armitage, University of Nebraska, with Dr. John Cole as Executive Secretary. Dr. Edward Bresnick, University of Massachusetts, will chair a comprehensive review of prevention research, with Dr. Jack Gruber serving as Executive Secretary. The review of the Drug Development Program will be chaired by Dr. Stuart Schreiber, with Dr. Vincent Oliverio as Executive Secretary. The review committee for the Genetics Program is in early stages of organization; Dr. Klausner, Dr. Livingston, Dr. Joseph Fraumeni, Dr. Knudson, and other members of the Executive Committee will be working to develop goals, the committee charge, and a roster of committee members.

Dr. Livingston gave the schedule for the reviews. The report of the Cancer Centers Program is expected to be completed by summer. April 8 is the scheduled start date of the clinical trials review, April and May start dates are anticipated for the prevention and drug development program reviews, respectively. Dr. Livingston explained that written reports are expected to be completed within 6 to 9 months from the start dates. Because

the issues addressed in the individual reports will overall, the BSA, working with the leadership and NCAB members, will have the responsibility of receiving and integrating the results of the reviews. Dr. Livingston looked forward to a partnership with the NCAB in this endeavor.

Dr. Livingston listed members of the Cancer Centers Working Group and their affiliations: Joseph Simone, Chair, Memorial Sloan-Kettering; Michael Brown, University of Texas (UT), Johnson Center for Medical Genetics; Deborah Collyar, Clinical Trials Information Project; Virginia Ernster, University of California, San Francisco; Judy Garber, Dana-Farber Cancer Center; Judith Gasson, Johnson Comprehensive Cancer Center, University of California, Los Angeles; Edward Harlow, Massachusetts General Hospital Cancer Center and Harvard University; Jean Harlow, UT M.D. Anderson Cancer Center; Richard Hynes, Massachusetts Institute of Technology (MIT) Cancer Center; Joseph Pangano, Lineberger Center for Cancer Research, North Carolina; Frank Pendergast, Mayo Clinic Cancer Center; Philip Sharp, MIT; Richard Schilsky, University of Chicago Cancer Center; Ralph Snyderman, Duke University; James Watson, Cold Spring Harbor Laboratory; Max Wicha, University of Michigan Cancer Center; and Robert Young, Fox Chase Cancer Center. NCAB representatives are Dr. Michael Bishop, Dr. Robert Day, and Dr. Sydney Salmon; Dr. Paulette Gray is the Executive Secretary.

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## **BOARD OF EXTRAMURAL SCIENTIFIC ADVISORS STATUS REPORT QUESTIONS AND ANSWERS**

Dr. Sigel asked for and received confirmation that the mission of the Cancer Centers Working Group is to evaluate the NCI's program.

At the request of Dr. Dickersin, Dr. Livingston defined "consumer" as a layperson who has a strong interest in the way in which cancer medicine and cancer research is carried out in the United States, and perhaps one who has had first-hand experience with the NCI and the way in which it fulfills its mission. Dr. Dickersin asked whether the NCI applies this as a standard definition for all groups. Dr. Klausner explained that this is a working definition that is used in the NCI's attempt to recruit representatives from different communities on each advisory and working group.

Dr. Dickersin recommended refinement of that definition to include the requirement that the consumer representative should be a person with cancer and should have a constituency to whom she or he can report. She emphasized the importance of two-way communication of these deliberations. Dr. Livingston pointed out that people who have been seriously discussed for membership on the program review working groups fall within the extended definition recommended by Dr. Dickersin. Ms. Brown agreed with the need for consistency in defining consumer representation. Dr. Sigel observed that the definition should be broadened to include others affected by cancer such as families, children, and spouses, and Dr. Rimer identified people at high risk genetically but without cancer as another interested consumer group. Dr. Klausner agreed to consider any recommendation of the Board that consumer representatives must represent an organization, but he pointed out that further definition as to type and size of organization would be needed. He pointed out that advisory groups, to be successful, bring together a broad range of perspectives--different vantage points, different communities--and a broad range of expertise to look at very specific issues. Reports by these advisory groups will be presented to and discussed by the Board and will receive wide dissemination. Rather than develop specific entrance criteria, Dr. Klausner suggested submitting the next few rosters generated by the NCI for Board consideration as to whether their representation of different viewpoints is acceptable. Dr. Wittes added that, for all advisory boards, the Institute chooses individuals on the basis of their personal qualities to represent diverse points of view, not on the basis of representing a constituency.

Dr. Dickersin agreed that these were valid points but she reiterated her recommendation that there should be one person on each board who has experienced cancer because of the different perspective that person can

bring to the table. She also emphasized the importance of having consumers disseminate these messages about the efforts of cancer scientists to diverse advocacy and support groups.

Dr. Bishop expressed a bias against a hard and fast definition of consumer representation, but agreed that access to a constituency is a good criterion for candidates, because they can get the message out that peer review is working, is legitimate, and is being done properly. Dr. Klausner pointed out that individuals already on boards were chosen, because they came to attention by their activism and participation in patient and patient advocacy groups.

Dr. Rimer concluded by agreeing that some refinement of the definition may be needed, but she expressed satisfaction that consumer representation has been accepted for all committees and the NCI has unilaterally recruited consumer representatives to every one of its review groups. She introduced Dr. Faye Austin, Chairperson of the NCI Extramural Advisory Board (EAB).

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## EXTRAMURAL ADVISORY BOARD

Dr. Austin thanked Dr. Rimer and members of the Board for the opportunity to present an update of the status of the EAB, noting that creation of internal advisory boards--both intramural and extramural--was one of many innovations since Dr. Klausner became the Director of the NCI. She referred Board members to distributed copies of the EAB charter and membership roster.

The EAB was created to provide a structured mechanism for extramural staff to communicate with the leadership of the NCI on the issues that affect their ability to manage and operate the extramural programs of the NCI. Communication is two-way in that the EAB provides advice in advance of policy approval on what might be impediments to new implementations. The group is working on ways to improve communication so that there can be better mechanisms for implementation of new policies.

The EAB has broad representation of the NCI staff, including extramural program administrators, program directors, extramural review staff, scientific review administrators, and grants and contracts management staff. Ex officio members are Dr. Alan Rabson, Deputy Director, the NCI; Dr. Kalt, Director, DEA; Mr. Philip Amoroso, Associate Director for Extramural Management, OD; and Mr. Steve Hazen, Chief, Extramural Financial Data Branch. Staff members are appointed for 3 years. The initial appointments were for 1, 2, or 3 years to set up a rotation mechanism for membership, and reappointment can occur only after a 1-year hiatus.

Dr. Austin commended the success of the EAB's Executive Secretary, Ms. Susan Waldrop, in distributing minutes to all staff. Minutes and agendas are circulated electronically in advance of meetings to permit adequate preparation for the meetings.

Since its institution, the EAB has reviewed and commented on new NCI policies related to the criteria for Method to Extend Research in Time (MERIT) awards and for use of RFAs, the AER, and the Performance Management System. Dr. Austin explained that the EAB will be looking for ways to get funding to the best science to take advantage of opportunities in the most timely way. The EAB will also be receiving information in real time from AER applicants, by way of AER program staff, as a guide to improving the new program. Proactive accomplishments of the EAB include recommending new NCI policies on Levels of Authority (LOA) for grant actions and recommending the development of the NCI Shannon awards. In other actions, the EAB briefed staff on new policies, established semiannual staff meetings with the NCI Director, compiled and distributed a resource list of extramural staff "computer experts", established a liaison with the NCI Information Resource Advisory Committee, and developed a priority list of EAB activities. The latter action satisfies the requirement set forth in the charter that the group establish its own agenda by identifying the issues that may be impeding the ability to serve the extramural scientific community, manage extramural staff activities, and ensure careful stewardship of Federal funds.

Currently, the EAB has established a subcommittee to streamline the NCAB grant review process for both staff



and NCAB members. Cochairs of this committee are Dr. Kirt Vener, DEA, and Dr. Grace Shen, Division of Cancer Biology (DCB). Dr. Shen has also had an opportunity to observe other councils, and this experience will be applied by EAB in its efforts to improve the timeliness and format of grant materials going to NCAB for review. A second subcommittee will address issues related to ensuring the most effective use of P01 grants for meeting the needs of the NCI and to streamlining the peer review process. This subcommittee will be chaired by Dr. David Irwin, DEA, and Ddr. Colette Freeman, DCB. Dr. Austin noted that the EAB would be reporting back to the NCAB on this issue. A third subcommittee is investigating ways to stimulate the submission of higher quality SBIR and Small Business Technology Transfer (STTR) grant applications and to streamline the process for both applicants for this committee.

Dr. Austin reported that communication with the extramural scientific community is a very high priority activity. Currently, the EAB is working to improve information dissemination from the NCI to the extramural community, enhance opportunities for feedback to the NCI, and increase opportunity for interaction with the NCI extramural staff.

Future activities will build on recommendations from the NCI streamlining report. Internal communication and interaction across all NCI programs will be improved, including program, review, and grants management components within the extramural divisions and across divisions. Opportunities will be sought for improving the co-funding process and procedures--for example, with the NIH Office of AIDS Research and Office of Research on Women's Health, as well as with other Institutes--to capitalize on research opportunities. Other future EAB activities will focus on improving and streamlining the contracts review process, scientific information management for programs activities, Institute and Program grant referral guidelines, and maintenance and enhancement of scientific knowledge of extramural staff. Dr. Austin concluded her update by noting that the EAB expected to be interacting with Board members and members of the BSA in these activities.

Finally, Dr. Austin reported that EAB would be sponsoring a series of activities to help new applicants deal with the grant application and review process. Focuses of the instruction will be how to submit the best possible application, the first time, to take advantage of the opportunities provided by the AER program, and how to increase the potential for submitting successful revised applications. Dr. Rimer suggested the DCPC series of workshops on grantsmanship for potential grantees as a good model for EAB's workshops.

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## EXTRAMURAL ADVISORY BOARD QUESTIONS AND ANSWERS

Dr. Becker noted the excellence of the introductory material about both the EAB and BSA, but he expressed concern with the statement that EAB was reviewing P01s to see how they "serve NCI programs", because that terminology seems to depart from the NCI's attempt over the previous 6 months to stimulate spontaneity in the extramural scientific community. Dr. Austin characterized Dr. Becker's perception as opposite to her intent, which was to indicate that the NCI is attempting to identify alternatives that will allow more flexibility so that those types of grants can be driven by the extramural community.

Dr. Bishop and Dr. Calabresi commended the presentations by Dr. Livingston and Dr. Austin as very pleasing to hear--the kind of rigorous evaluation and reaching out to the extramural community for advice that they had hoped to see.

Dr. Klausner stated that he liked the idea of intramural and extramural advisory boards and that both is really only beginning, but the NCI is moving toward a culture that responds to issues such as those raised by Drs. Becker and Calabresi. Dr. Rimer added that NCAB members can see that they are an integral part of those review groups.

Dr. Rimer made three final comments to wrap up NCAB business. She announced that she and Dr. Kalt are

working on subcommittee scheduling to avoid cancellation of subcommittee meetings to accommodate the types of executive meetings the Board wants. Ske asked for NCAB member suggestions for the role statement so that several versions can be ready for review at the upcoming Board retreat. She announced that Board members, including retiring members, would receive information about the retreat and word about the May meeting as soon as possible after her planning meeting with Dr. Kalt the following week. Finally, Dr. Rimer thanked members who are retiring from the Board for their participation in this meeting. She adjourned the 97th National Cancer Advisory Board meeting at 12:51 p.m.



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