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

Summary of Meeting
February 13-14, 2001

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND

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The National Cancer Advisory Board (NCAB) convened for its 117th regular meeting on Tuesday, February 13, 2001, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public from 9:00 a.m. to 4:00 p.m. The meeting was closed to the public from 4:00 p.m. to 5:15 p.m. The meeting was reopened to the public on Wednesday, February 14, 2001, at 8:45 a.m. until adjournment at 11:45 a.m. Dr. Phillip A. Sharp, Chair of the NCAB, presided during both the open and closed sessions.

NCAB Members

Dr. Phillip A. Sharp (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. Richard J. Boxer
Mr. Stephen C. Duffy
Dr. Ralph S. Freedman
Dr. James H. French
Dr. Elmer E. Huerta
Dr. Howard K. Koh
Dr. Frederick P. Li
Dr. Susan M. Love
The Honorable James E. McGreevey
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Ms. Ellen L. Stovall

President's Cancer Panel

Dr. Harold Freeman (Chairperson)
Mrs. Frances Visco

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Dr. Michael A. Babich, U.S. CPSC
Ms. Raye-Anne Dorn, DVA (for Dr. T.G. Patel)
Dr. Peter Kirchner, DOE
Dr. Alison Martin, FDA
Dr. Hugh W. McKinnon, EPA
Dr. John M. Powers, DOD, OASD, HA
Dr. Anita Schill, NIOSH

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Ms. MaryAnn Guerra, Deputy Director for Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences

Dr. Carl Barrett, Director, Division of Basic Sciences
Dr. Joseph Harford, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Dr. Shalini C. Vallabhan, American Cancer Society
Ms. Mary Mitchell, American College of Obstetricians and Gynecologists (for Dr. Stanley Zinberg)
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Ms. Kristin Simonson, American Society of Therapeutic Radiology and Oncology
(for Ms. Nancy Riese Daly)
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Mr. Carl Dixon, Kidney Cancer Association
Ms. PaulaAnn Rieger, Oncology Nursing Society

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DAY ONE – FEBRUARY 13, 2001

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING—DR. PHILLIP SHARP

Dr. Phillip Sharp, Institute Professor, Center for Cancer Research, Massachusetts Institute of Technology, and Chairperson, NCAB, welcomed guests representing liaison organizations. He noted that the NCAB has added a new liaison organization, the National Coalition for Cancer Survivorship, represented by Ms. Ellen Stovall. He also welcomed members of the public and invited them to submit to Dr. Marvin Kalt, Director, Division of Extramural Activities, NCI, and Executive Secretary, NCAB, comments regarding items discussed during the meeting in writing and within 10 days.

A motion was requested and made to approve the minutes of the December 2000 NCAB Meeting. They were unanimously approved by the Board.

Dr. Sharp asked the Board members to join him in congratulating Dr. Klausner on his reappointment as Director of NCI.

II. FUTURE BOARD MEETING DATES—DR. PHILLIP SHARP

Dr. Sharp called Board members' attention to future meeting dates listed in the agenda. Dates have been confirmed through 2002.

III. REPORT OF THE DIRECTOR, NCI—DR. RICHARD KLAUSNER

Legislative Update. Dr. Klausner began his remarks with an overview of changes in the leadership of Congressional Committees whose actions affect the NCI. He reported that on December 29, 2000, legislation creating a new National Institute of Biomedical Imaging and Bioengineering was signed into law by former President Clinton, and the NIH is now developing this Institute's mission statement and organizational structure. Dr. Klausner said that he planned to report further on this topic at a future NCAB meeting because significant interactions between this new Institute and the NCI are anticipated. Legislative issues that will be closely watched and reported on at future NCAB meetings include the Patient's Bill of Rights, provisions that affect access to clinical trials, and issues related to stem cell and fetal tissue research.

NCI Budget Update. Dr. Klausner explained that the appropriations bill for the current fiscal year was signed on December 21; until that time, the NCI had been operating under a series of continuing resolutions. Currently, he noted, the Institute is under a hiring freeze. Dr. Klausner expressed confidence that the new Secretary of Health and Human Services, former Wisconsin Governor Tommy Thompson, will continue his strong support for biomedical research, for biotechnology development, and for the NIH in particular. Dr. Klausner reported that the current year's budget for the NCI, $3.757 billion, represents a 13.5 percent increase over the previous year's budget of $3.3 billion. He reminded the audience that, at the last meeting, the Board passed a resolution calling for management and administrative funds for the Institute to amount to 5 percent of the overall budget. He noted that the Research Management and Support (RMS) portion of the current budget contained a 16.5 percent increase. The increase raised the RMS portion of the overall budget to 3.6 percent. Dr. Klausner stated that the Grants Program, which is

the largest part of the NCI budget, currently contains $1.6 billion for the Research Projects Grants (RPG) pool of investigator-initiated research.

The Institute predicts that 29 percent of submitted grants will be funded, compared with 28 percent last year. He noted that the 4,485 research grants that the NCI expects to award this year represent an increase of 265 grants over last year—the largest number of grants ever awarded by the Institute. Dr. Klausner explained that before any new grants can be funded, 25 percent of the budget increase is committed to the "out years" of 3,254 Type 5 grants, which are continuing grants whose costs rise each year. He added that the pool of Type 5 grants is larger this year, reflecting the growth in the number of grants over the last several years. Dr. Klausner explained that the payline for competing R01 grants has been set at the 22nd percentile, the same as last year; however, a larger number of grants will be funded because the applicant pool is increasing in size. With the increasing average cost of grants, he continued, the dollars spent within the payline this year for about 780 new grants will increase by 17 percent. The average cost requested for the 3,200 applications received is up about 10 percent; however, the average cost for those applications placed within the payline by the study sections is up more than 15 percent, and the average cost increase for Type 2 grants is 45 percent. There is also a trend toward more grants of over a million dollars. Dr. Klausner stated that they were uncertain why the increases were occurring, but that they were looking at the matter carefully. These shifts continue to present challenges for the NCI as it makes decisions on numbers of grants funded, success rates, dollars per grant, etc. The changes in the average cost of grants, Dr. Klausner continued, have caused the NCI to shift about $12 million from the rapidly diminishing Director's Reserve into the RPG pool. Many of the more expensive grants fall into the area of population studies. This has led to discussions with Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), and Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), about analyzing this phenomenon and developing cost management guidelines for NCI staff and for reviewers. Dr. Klausner said that when this information has been collected, he will report back to the NCAB, and particularly to the Subcommittee on Planning and Budget, on this important topic.

Dr. Klausner stated that the changes in average costs of grants have also led to changes in how the NCI conducts downward negotiation of grants. It was felt that an across-the-board cut would have a disproportionate impact on smaller grants. After extensive discussions with the Executive Committee, it was decided that there will be an 18 percent reduction for grants greater than seven modules, at $25,000 per module. For all grants below that level, there will be a 12 percent reduction from the requested level. Dr. Klausner explained that previous reports of downward negotiations were based on amounts recommended by reviewers; the new reductions of 18 and 12 percent are based on requested levels, which are traditionally about 5 percent higher than recommended levels. In effect, he added, these reductions are lower than last year's, in keeping with the NCI's movement toward lowering downward negotiations. Dr. Klausner explained that a priority score has not been set for P01 applications. Each will be paid on a case-by-case basis. The total dollars committed will be held to the proportion of P01s to R01s in last year's RPG pool. A success rate of about 40 percent is expected for this year's 89 P01 applications, which is similar to last year's success rate for 100 applications. Dr. Klausner reported that an additional $48 million, representing an 18 percent increase, has been budgeted for Cancer Centers and the Specialized Program of Research Excellence (SPORE). Cancer Centers will receive an additional $30 million, for a total of $190 million. This includes an increase from 60 to 61 Centers, plus 5 planning grants. The average cost of a core grant renewal has risen from $2.3 million to $3.5 million. SPOREs, Dr. Klausner noted, are growing quite rapidly; this year, there will be a 36 percent increase in funding for SPOREs.

One reason, he added, is the NCI's 5-year plan to open the SPOREs to all cancer sites. The NCI, Dr. Klausner stated, expects up to nine new SPOREs this year, including programs covering prostate, ovarian, lung, gastrointestinal/urinary, and skin cancers. There will also be about $4 million in supplements to SPOREs to work together in areas such as technology access, biomarker and prevention activities, and expanding high-priority clinical trials.

In the training area, Dr. Klausner noted, there will be a 23 percent increase in the K program, with the number of K awards increasing from about 260 to about 320. A new program, the K05, is an established investigator award in cancer prevention, control, and behavioral and population research. While the number of National Research Service Awards (NRSAs) is not changing, the stipend levels for these will increase about 10 percent, to $16,500 per year per individual. Dr. Klausner stated that funding for minority training will increase significantly. There is a new focus on partnerships between minority-serving institutions and Cancer Centers. This effort is being undertaken in collaboration with the new National Center for Research in Minority Health and Health Disparities. Dr. Klausner noted that the budget for minority-directed training activities will increase from $19.5 million to $35 million. He said there would be a report on the new partnership programs between Cancer Centers and minority-serving institutions at a future NCAB meeting. Dr. Klausner reported on a small, experimental RPG funding project, a competitive application process for "activities to promote research collaboration," or APRCs. This program was initiated in 1998, and the Executive Committee has agreed to continue to support it for 3 years. These grants support novel scientific collaborations among NCI grantees, as well as meetings and workshops. In the first 3 rounds, there have been 68 requests for these collaborations—with an average number of 3 investigators—and there have been 5 workshops. Dr. Klausner concluded his budget report with a comparison of the FY 2001 distribution of new dollars with the strategic planning described in the 2001 Bypass Budget. The 2001 budget amounts to 91 percent of the budget requested in the Bypass Budget. Of the 443 million new dollars received, as mentioned earlier, $113 million went to pay out obligations on Type 5 grants; of the remaining $330 million, about 85 percent is aligned with areas of priority in the Bypass Budget. This, Dr. Klausner noted, is similar to the proportion in last year's budget. About 55 percent went to areas of the Challenge section of the Bypass Budget (equaling 31 percent of requested dollars in the Challenge section) and 30 percent to Areas of Extraordinary Opportunity (or 26 percent of requested dollars). Dr. Klausner noted that the Institute was able to fund a majority of what it wanted to do in the areas of clinical and translational research, and had perhaps had the least success in expanding the National Clinical Trials Program.

Resources. Dr. Klausner reminded the Board of his description, during the December NCAB meeting, of the NCI's *Research Resources* Web site, which has been called the "Cancer Rolodex" by the journal *Science* and is known within the NCI as the Institute's "*Whole Earth Catalog*." The latest version, he noted, was launched 1 month ago and has had about 40,000 visitors since then. New entries include an online training module for researchers using human subjects; enhancements to the NCI database browser for searching over 250,000 compounds; a new risk communication bibliography; and an online guide for tailoring health messages. The site, Dr. Klausner continued, also includes Special Populations Network resources and links to cancer information directed to special populations. Dr. Klausner described a new program to disseminate new technology and support translational research. The Tissue Array Research Program (TARP) is a collaboration between the NCI and the Human Genome Institute. Its goal is to create multi-tumor tissue arrays. The archive that has been developed comprises microassay glass slides of tissue samples, including normal tissue, normal cell lines, and tumor samples. A single slide can

contain more than 500 tissue samples. Dr. Klausner reported that these samples will be available for $20 per slide, plus shipping.

NCI's Surveillance Program. Dr. Klausner described changes in the Surveillance Epidemiology and End Results (SEER) program that have been initiated in response to input from a Surveillance Implementation Group and a report prepared by the National Academy of Sciences' (NAS) Institute of Medicine (IOM) on minority research and health disparities. These initiatives were designed to increase the monitoring of specific populations, including non-Mexican Hispanic Americans, Americans below the poverty level, rural Americans, African Americans, and Native Americans and Alaskan Natives. The four areas of the country that have been added to the SEER program to accomplish these objectives include the remainder of the State of California and the States of Kentucky, Louisiana, and New Jersey. The new areas have increased SEER coverage by 157 percent for rural areas; 101 percent for Americans below the poverty level; 96 percent for African Americans; 75 percent for total Hispanics; 71 percent for non-Mexican Hispanics; 45 percent for Asian/Pacific Islanders; and 36 percent for Native Americans and Alaskan Natives. The total SEER population has increased by almost 90 percent, from 34.5 million Americans to more than 65 million, moving from 14 percent of the population to 26 percent. SEER now covers 59 percent of the Asian/Pacific Islander population; 42 percent of the Native American and Alaska Native population; 44 percent of the total Hispanic population; 34 percent of the non-Mexican Hispanic population; and 24 percent of the African American population. Dr. Klausner acknowledged that SEER, even with this increased coverage, cannot provide all of the information needed about the burden of cancer. He explained that SEER needs to be supplemented with other data, particularly from the States for which the Centers for Disease Control and Prevention (CDC) is responsible. About a year ago, Dr. Klausner related, a Memorandum of Understanding was signed for strategic planning and development of unified standards so that data can be pooled between the SEER program and the CDC National Program of Cancer Registries. This collaboration, he stated, is working very well. Dr. Klausner explained that the SEER program is the centerpiece of a larger research structure that includes the ability to create linked data sets that provide unique research opportunities. He explained that the NCI has been developing rapid response studies which, to date, have been called SEER Special Studies; but which are evolving into rapid responses to various observational epidemiological data. Dr. Klausner stated that these linked data sets and rapid response studies are helping to explain certain trends in behavior, health care systems, and new technologies. One example is the Prostate Cancer Outcome Study, which is currently the best source of data in the world related to the implications of different prostate cancer treatments. Dr. Klausner observed that the ability to link SEER and Medicare databases will make it possible to ask questions about quality of care and costs of care. Another example of these kinds of linkage studies, he added, is a recent article in the *New England Journal of Medicine* showing that African Americans are less likely to get curative resection surgery for lung cancer. Dr. Klausner mentioned, as a final example of this type of effort, the California Health Interview Survey, which is supported in part by the NCI. This will be an in-depth survey of access to care, socioeconomic factors, cancer risk, and screening behaviors in a State that is now fully covered by SEER.

Preview of Cancer Statistics. Dr. Klausner reported that the NCI is in the process of concluding the analysis of 1998 data. The NCI, he said, has for the past 4 years collaborated with the CDC, the American Cancer Society, the National Center for Health Statistics (NCHS), and the North American Association of Central Cancer Registries to produce an annual report on cancer statistics. The target date for release of this year's report is April 2001. Dr. Klausner thanked and recognized Ms. Brenda Edwards and her team for providing oversight of the SEER program and for providing advice and assistance in

interactions with other registries throughout the world. Each year, the report on cancer statistics has focused on an area of special emphasis, such as lung cancer and smoking or, in last year's report, colorectal cancer. This year's report, Dr. Klausner said, will focus on cancers whose burden is increasing. While overall cancer incidence and mortality continue to fall, cancers that are increasing make up about 12 percent of the cancer burden. They include non-Hodgkins lymphoma, liver cancer, adenocarcinoma of the esophagus, and several other rarer cancers. Dr. Klausner presented slides illustrating the declining trends in overall cancer statistics, which differ between men and women and between African Americans and white Americans. In terms of cancers whose mortality rates are going up, Dr. Klausner focused on non-Hodgkins lymphoma, noting that the rate of increase is slowing, although the causes of the increase and the slowdown are not understood.

Dr. Klausner then presented an overview of survivorship statistics based on collaborations between the Office of Cancer Survivorship, the SEER program, and the Applied Research Branch. He recommended that anyone interested in survivorship statistics visit the Office of Cancer Survivorship's Web site. Dr. Klausner presented data extrapolated from the Connecticut SEER registry suggesting that there are between 8.5 and 9 million cancer survivors. Pointing out that the Connecticut sample is not likely to be representative of the entire Nation, he then presented selected newer data from the Office of Cancer Survivorship Web site based on analysis of the entire SEER data set, including an estimate of 7.1 million cancer survivors. Dr. Klausner noted that these data use definitions of survivorship that differ from those used in previous extrapolations; the previous estimate is based on 54-year prevalence, whereas the newer estimate is based on 20-year prevalence. He reported that 60 percent of cancer survivors are over 65 years of age, and a third are between the ages of 40 and 60. He showed data indicating that from 0 to 5 years, there are more male than female survivors, but that this trend is reversed at 15 to 20 years. Dr. Klausner stressed that this difference is influenced by deaths from other causes, incidence trends, and other factors. Dr. Klausner provided an overview of support for cancer survivorship research grants during the past 4 to 5 years. In 1996, about $6.6 million was spent on such grants, and now that figure is over $32 million. The largest areas of investigation in survivorship, he added, are quality of life and health behavior interventions.

Personnel and organizational changes. Dr. Klausner announced that Dr. Edison Liu, Director, Division of Clinical Sciences, will be leaving the NCI to lead a human genomics program in Singapore. In conjunction with Dr. Liu's departure and in response to recommendations from an intramural working group, Dr. Klausner reported, the Institute has come to the conclusion that by having the Division of Basic Sciences separate from the Division of Clinical Sciences, a gap has been created that needs to be bridged. In response, there will be a major restructuring of the intramural research program and the creation of a new entity within the NCI to be called the Center for Cancer Research. This unit, Dr. Klausner announced, will be headed by Dr. Carl Barrett. At a future NCAB meeting, he said, there will be a presentation on the vision of this new Center and a description of the new approach to integrated cancer research linking technology development, basic research, clinical research, and translational research.

V. INTERPRETATION OF HUMAN GENOME SEQUENCE DATA—DR. ERIC LANDER

Dr. Eric Lander, Director of the Whitehead Institute/MIT Center for Genome Research, Cambridge, MA, gave a synopsis of the exciting events of the previous day—Monday, February 12, 2001—which marked the public release of the human genome sequence. The journal *Nature* published

the seminal article in its February 15 issue and thus has launched the era of postgenomic science. On Monday morning, there was a press conference at the Capital Hilton, Washington, DC, at which scientific presentations and reporter questions helped unveil the significance of the experimental developments detailing the human genome. The subsequent historic symposium at Masur Auditorium at NIH in Bethesda, MD, fueled a celebration of the news and the accomplishments among the scientific community. Drs. Francis Crick and James Watson, who in 1953 codiscovered the structure of DNA, spoke, respectively, about the tremendous advances in science and about the initiation of the Genome Project in the late 1980s. Other scientific leaders at the forefront of genomic research talked on different aspects of the human genome and its potential for increasing scientific knowledge. From its initiation, the human genome project paralleled the endeavor to put a man on the moon with great confidence for success and a certain vagueness in technical detail. The belief in the power of science, scientific cooperation, scientific organization and vision propelled the proposal into reality. Dr. Lander furnished details of the information provided and implications generated by the human genome sequence data, and he enthusiastically reviewed the process of achievement.

Methods of Approach. A 3-year pilot project began in 1996 to lay the groundwork of tools, ideas, and strategies. In the United States, the NIH and the Department of Energy worked closely with groups in England, France, Germany, Japan, and, eventually, China. The 3 years allowed for important shifts in the way the biology was performed, incorporating robotics to improve productivity and reproducibility. Currently, at the Genome Center at the Whitehead Institute, 120,000 clones a day can be analyzed—i.e., grown, purified, and the sequencing reactions set up. A bank of commercial sequence detectors analyzes 65 million letters of DNA sequence per day. In 1999, the successful pilot project helped initiate a large scale-up endeavor. This was very much a collaborative effort; in all, an international consortium of 20 groups worked on sequencing the human genome, with the largest sequence contributions coming from the Washington University, St. Louis, Genome Center; the Sanger Center in Cambridge, England; and the Genome Center at the Whitehead Institute. At the start of 1999, approximately 10 percent of the sequence had been determined; within 12 to 14 months, approximately 90 percent of the genome was known. At that time, a private company sought to compete with the public enterprise and propagated the idea that the public sequencing endeavor was inefficient. Dr. Lander said that competition almost always spurs higher productivity, but in the end, this company caused an acceleration of only 6 to 9 months, while distinctly contributing to stress levels. Specifically, he noted that the statements in the media about a 3- to 5-year acceleration of the genome project involved moving the goalposts. The initial target date concerned the completion of a finished sequence; this goal is still a few years off, because closing gaps in the genome is a slower task. Part of the stress involved numerous press releases that capitalized on the idea of a race between the two endeavors. Ultimately, a brilliant solution was realized through a joint declaration of victory by both groups that 90 percent of the human genome was completed. No annotation had been done, but this announcement satisfied the need for an "end to the race." Obviously, a lot of work was still necessary to begin analyzing the human genome. In the past 6 months, a group of 50 computational biologists in the international Genome Analysis Group assembled the components of the genome. Approximately 900 gaps were found that require additional clones to uncover the sequence data. However, of the data currently in the database, 91 percent of the bases are accurate at the 99.99 percent level. Moreover, annotation of the sequence has begun and the information hidden within is beginning to unfold.

Results to Date. The human genome lacks uniformity in that vast tracks are enriched for the nucleotides guanine (G) and cytosine (C). The compositional heterogeneity along the sequence provides

GC-rich islands amidst G-poor deserts. A paper accompanying the sequence report in the February issue of *Nature* has mapped the physical band traits of the chromosomes to regions of different nucleotide composition. Different repeat elements appear frequently in one or the other type of DNA region. Indeed, most of the genome consists of repeat elements, and only one to one and one-half percent of the genome appears to encode for proteins. The so-called "junk" DNA reveals amazing scientific stories. For example, 50 percent of human DNA clearly traces to transposable elements, which are of four types: long interspersed nuclear elements (LINEs), short interspersed nuclear elements (SINEs), long terminal repeat (LTR) retroposons, and DNA transposons. LINEs encode for proteins whose function is to insert their own message RNA into the genome in the nucleus. SINEs encode RNA that can use LINE proteins to move them into the nucleus (so-called "parasites on the parasites"). LTRs include *gag* and *pol* genes necessary for infectivity by retroviruses and are thought to be the origin of retroviruses that went on to pick up a coat protein. Finally, DNA transposons encode proteins that act directly on their parental DNA sequences to move them around within the genome. Analyzing the occurrence of transposable elements has enabled construction of an entire family tree. Certain elements are in the common ancestor that humans share with fish; others link humans with mice; others appear similar in humans and chimpanzees; and so forth. A story of our ancestry is written not in genes, but in our "junk" DNA. An interesting finding is that the rate of transposition by all four types of elements has plummeted in the past 30 to 40 million years. Transposable elements seem to be dying out in the human genome, although they are active in the mouse genome. No one knows why. A further interesting finding is that repeat regions tend to congregate in adenine (A)- and thymine (T)-rich regions, presumably so as not to disrupt their hosts' genes, which concentrate in the GC-rich regions. All transposable elements, with the exception of the SINEs, follow this rule. SINEs occur in high frequency near DNA sequences defining genes; however, because SINE elements use LINE proteins to become integrated in the genome, they theoretically have the same movement as LINEs. By analyzing sequences throughout the ages, it appears that evolution is reshaping the distribution of these apparently useless parasitic elements to cause a 13-fold enrichment over 25 million years. These elements may, instead, be important symbiotes of genes and may be involved in regulation of protein translation.

A third finding is that, because different areas of the genome have different mutation rates, analyzing repeat elements that have transposed to different genomic regions can help reconstruct population migration in a much more powerful way than was done previously. Analysis of the genes within the genome is difficult because so few genes are encoded. The total estimate of 35,000 genes is two-thirds less than anticipated (by a purely numerical calculation) and less than twice the number of genes in the lowly nematode. Dr. Lander noted that this affront to human dignity may be lessened by understanding that the human gene undergoes alternative splicing to make two to three times as many products as are produced by a worm gene. Moreover, protein domains can be put together in new ways such that the cell surface molecules and intracellular signaling mechanisms that are highly evolved in humans can be created using a diverse array of architectural combinations. The analysis of the human genome has also revealed that 223 of the genes may have been derived from bacteria. Furthermore, comparison of the human genome with the sequence currently available from the mouse shows an amazing conservation in a set of regulatory genes called the HOX clusters. Many important developmental questions will be addressed with further analysis of the human genome.

Conclusions. Dr. Lander stated that the advent of a postgenomic era means that science will be approached differently. Rather than being initially driven by theories, scientists can address the huge amount of data now available to them and then focus on developing and testing hypotheses. An area of

particular interest is certainly the nature of human genetic variation and elucidating its role in disease. The limited number of genes in the genome aids this goal. In addition, ancestral gene segments can be used to develop linkage disequilibrium maps to trace disease; ancestral segments act as markers and have turned out to be bigger within the genome than originally thought. Dr. Lander said that once the sequence of the human genome is complete, a biologic "periodic table" can be described. This table will radically transform biomedical research in the 21st century much as the periodic table changed chemistry in the 20th century. Not only will all the elements of the table be known, but so will the variants of genes, which are analogous to the isotopes of the chemical elements. Dr. Lander credited the success of the project to the cooperation of many people throughout the world. He emphasized that the unique infrastructure created will need to be further expanded and developed to capitalize on "big science" while not limiting the creativity of individual scientists. The list of infrastructure-building projects includes compiling information on genetic variation, sequencing more organisms for comparison (especially regarding regulatory regions), and producing all the full-length cDNAs for the human genome.

Questions and Answers

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center and President and Director, American Society of Clinical Oncology (ASCO), wondered how Incyte Genomics, Inc., could be offering for sale 120,000 genes when the estimated number of genes from the sequence data is only approximately 35,000. Dr. Lander observed that although both Celera and the public sequencing endeavor came up with an estimate of 35,000 genes, others claim to have identified a much higher number of human genes. Technically speaking, genes lacking homology in other species and never expressed in the EST databases may have been missed. Dr. Lander added that in practical terms, direct analysis of discrepancies in the numbers of genes in Chromosome 22 have only resulted in the identification of a small number of genes. A similar margin of error across the entire genome will not account for the levels of differences currently claimed. Direct testing will settle this issue.

Dr. Ivor Royston, President and CEO, Sidney Kimmel Cancer Center, raised the question of whether the public database can be as easily navigated as Celera's database. The concern was that the value of the public genome database would be lost without user-friendly browsers. Dr. Lander paralleled his use of Microsoft's wordprocessor with the value-added browsers produced by industry; both are commercially available tools to help people do their work. Although a robust investment in bioinformatics in the public sector would help in encouraging the private sector to supply scientists with affordable, standardized choices, the currently available public browsers are sufficient for anyone to access the genome information.

A third question, asked by Dr. Frederick P. Li, Chief, Division of Cancer Epidemiology and Control, Dana-Farber Cancer Institute, stimulated discussion about the number of genomic samples that are needed to study a particular cancer, such as lymphoma. One answer was that sample size depends on the research question and what the study reveals in terms of identifying subsets of lymphoma. For a global perspective on the expression pattern of lymphoma, 50 to 100 samples may suffice, but for identifying the active signaling pathway for each subset of lymphoma and the inherited components in each subset, thousands of samples may be required. A final question centered on the differences between human populations. Dr. Harold Freeman, President and CEO, North General Hospital and Chairman, President's Cancer Panel, wondered whether there would be merging between the fields of sociology,

anthropology, and human genomics. Dr. Lander emphasized that while humans are 99.9 percent identical, the differences in alleles and, in particular, ancestral segments will prove useful in identifying disease-related genes. He noted that the small differences in population structure could be of tremendous advantage for biomedical research.

V. AMERICAN ASSOCIATION FOR CANCER RESEARCH UPDATE—DR. TOM CURRAN

Dr. Tom Curran, Chairman, Department of Developmental Neurobiology, St. Jude Children's Research Hospital, and President, American Association for Cancer Research (AACR), described the AACR as the organization for the cancer researcher. The Association has 17,000 members worldwide and strongly emphasizes scientific excellence in research. The mission of the AACR, Dr. Curran said, is to prevent and cure cancer through research, education, communication, and collaboration. A major strength of the AACR is its cross-disciplinary communication, which creates a powerful synergy for cancer research. New horizons for the organization include: (1) oncogenomics and the impact of new genome knowledge on cancer treatment and prevention; (2) bioinformatics; (3) recruitment of scientists from other disciplines into the cancer research field, especially mathematicians and physicists; (4) chemical biology, which represents new approaches to chemistry, turning chemicals into genetic tools; (5) biological imaging; (6) stem cell biology; (7) new molecular targets for drug development; and (8) mouse models to allow the testing of ideas about cancer-related genes in a physiological setting. Dr. Curran outlined AACR's priorities for the coming years. These include developing collaborations with other scientific disciplines, continuing to offer education and training opportunities, exploiting new information technology, and promoting international communication and collaboration. Initiatives in support of these priorities include a scientific retreat, which will bring together 30 leaders in the cancer research field to discuss the status of and prospects for cancer research. Other initiatives recently established or under development are standing scientific committees to strengthen the scientific profile of the AACR, task forces with very specific functions, scientific working groups, and councils representing young members, women, and minorities in cancer research.

Dr. Curran explained that the AACR's communications activities follow two tracks. One track includes public education to increase awareness of cancer research progress and to promote advocacy for increased support for cancer research. Other public education activities include Congressional outreach on science policy and two new initiatives at AACR annual meetings: the AACR Public Forum/Ask the Expert and the Scientist-Survivor program. Ask the Expert sessions provide one-on-one interactions between leading scientists and members of the public who can ask questions about any aspect of cancer and about the latest information on clinical trials. The Scientist-Survivor program allows top scientists to provide information on the latest findings in cancer research, and scientists in turn are educated about the perspectives of survivor advocates. The organization's second communications track is its scholarly publishing activities. AACR currently publishes four major journals: *Cancer Research; Clinical Cancer Research; Cancer Epidemiology, Biomarkers and Prevention;* and *Cell Growth and Differentiation.* All three journals are available online. This year, AACR will launch a new journal on molecular cancer therapeutics. AACR's Web site, www.AACR.org, reflects the two communications tracks. A track for members includes the four journals, specialized electronic publications, and Webcasts of some annual meeting sessions and virtual meetings. A track for the general public is under construction.

With the support of the NCI, AACR sponsors workshops on such topics as Methods in Clinical Cancer Research, Molecular Biology in Clinical Oncology, and Histopathology of Cancer. Dr. Curran listed Molecular Epidemiology, Cancer Genetics, Translational Research, Biostatistics, and Behavioral Epidemiology and Cancer Prevention as topics for future workshops. Dr. Curran indicated that these topics match well with existing NCI support programs and would provide a continuum of education and training opportunities. Recently, the AACR helped launch the Alliance of World Cancer Research Organizations, which held its first summit in Bangkok on December 3, 1999. The Alliance is designed to develop initiatives on an international scale to accelerate progress against cancer and to apply research results from the United States to other environments. Dr. Curran noted that education and training are high-priority components of the Alliance and perhaps the major reason for convening the international organizations. Increasing funding for cancer research, improving communication and access to information, developing cancer registries and tissue banks, addressing the need for clinical trials in diverse environments, promoting screening and prevention, and establishing an international continuing medical education (CME) accreditation system are among other top priorities. Dr. Curran added that the AACR could serve as a catalyst for discovery and innovation by bringing together the various constituencies of the Alliance. Noting that the AACR and the NCI enjoy a close association, Dr. Curran said that the AACR has made eight presentations to the NCAB since 1991. The two organizations held a meeting on molecular targets in November 1999, which aroused great interest from both industry and academia. A second meeting in association with the NCI and the European Organization for Research and Treatment of Cancer (EORTC) will be held in October 2001. Other examples of the AACR's partnership with NCI include NCI grants to junior investigators to attend AACR annual meetings and special conferences, and jointly sponsored educational workshops.

Dr. Curran indicated that the AACR commissioned a poll on Americans' attitudes toward cancer research in August 2000. AACR members were surprised by the responses. In response to a question as to which illness respondents worried about most, 48 percent named cancer, and 15 percent named heart disease. Eighty percent of respondents indicated that a family member or close friend had cancer. But when asked the odds of developing cancer during their own lifetimes, 24 percent said the odds were 1 in 1,000, and 26 percent said 1 in 100. Dr. Curran pointed out that the actual chance of developing cancer is 1 in 2 for males and 1 in 3 for females. Even with this level of denial and fear of the disease, he said, 70 percent of respondents wanted the Federal Government to at least double the current spending for research to find a cure for cancer, and 46 percent wanted to triple spending. Dr. Curran said that although the cost of cancer in terms of human suffering cannot be measured, the costs of the productivity loss, illness, and premature death due to cancer were $107 billion in 1999. The latest estimates for these costs are $180 billion in 2000. The total could reach as high as half a trillion dollars by 2010. These figures illustrate the enormous scale of the problem and the extent of human suffering. Dr. Curran emphasized that although the remarkable pace of scientific discovery is encouraging, the challenge remains to accelerate progress with the highest level of science possible. Dr. Curran concluded his presentation by stating that the AACR looks forward to continuing to work in partnership with the NCI to prevent and cure cancer.

Questions and Answers

Dr. Norton underscored the importance of the AACR in the total picture of the fight against cancer. He pointed out that the AACR, ASCO, and NCI have much in common, and he stressed that these organizations working together can do a better job than they can working individually. Dr. Curran replied

that he was looking forward to more opportunities for the AACR and ASCO to work together in the future.

VI. REPORT ON GENDER AND MINORITY ACCRUAL TO NCI TRIALS—DR. MARVIN KALT

Dr. Kalt explained that one of the authorization acts that governs the NCI is the NIH Revitalization Act of 1993. This Act calls for a biennial report concerning the accrual of women and minorities to clinical trials to be made to advisory councils within NIH, including the National Cancer Advisory Board. The language of the Act defines clinical trials very broadly, encompassing virtually all epidemiologic, treatment, and behavioral studies. The NIH report is centrally overseen by the Office of Research on Women's Health.

Pre-award Activities. Dr. Kalt indicated that the first step in implementing NIH policies on gender and minority accrual consists of health scientist administrators working with grant applicants to disseminate the requirements. The requirements are widely available; they are published in the *NIH Guide* and the Public Health Service Application Kit and are featured on NCI and NIH Web sites. NCI extramural staff are kept up to date via trans-NIH education programs and desktop distribution of policies and procedures. Peer reviewers, who also receive instruction on policies, include plans for recruiting appropriate populations of women and minorities as part of the merit evaluation of the proposed research. If peer reviewers have concerns, bars to the award are put in place. NCI staff then work with applicants to make revisions and ensure that accrual plans match the requirements for appropriate representation. Applications with bars are presented to the NCAB in closed session, and NCI staff report to the NCAB on how the bars were subsequently resolved. In 1999, 26 applications that required intervention to bring them into compliance with NIH's accrual policy were funded.

Post-award Monitoring. Grant recipients are required to report annually the actual accrual, and they are encouraged to list trials in the Physician Data Query (PDQ) system. The actual accruals are reviewed by each funding division within NCI and entered into the Central Data Collection software. If the actual accrual for an individual protocol diverges from the original plan, NCI Grants Management staff provide oversight, advice, and assistance. Finally, staff work with awardees to disseminate findings and encourage new studies.

Reporting. Dr. Kalt indicated that data on gender and minority accruals are required to be reported in an aggregate format, which includes all Phase III clinical trials—whether treatment, behavioral, or epidemiologic in nature. Overall treatment trial data are well balanced for gender and minority distribution within these trials. Individual trials vary considerably, and large population-based screening trials tend to swamp the aggregate data. While overall accrual has been successful, challenges remain. One major challenge is the accrual of minorities for clinical trials where subjects have no known disease—e.g., prevention and screening trials. NCI funds basic research to address methodologic issues and provide scientists with evidence-based tools with which to improve recruitment. NCI staff also conduct outreach programs to disseminate this information to the research community and publish information on ways to address barriers to accrual.

Results. Dr. Kalt showed the Board members the 1998 statistics on NCI enrollment for extramural research protocols by race/ethnicity. More than 2 million subjects were enrolled in these

studies. More than half were minorities—a large number relative to the cancer burden for many of the racial/ethnic groups. Statistics by gender showed that women were overrepresented relative to men, a disparity due to large-scale epidemiologic studies on breast cancer, ovarian cancer, and other organ-specific diseases. Among racial/ethnic groups, Asians were heavily overrepresented: this constituted 20 percent of the enrollment but comprised about 1 percent of the U.S. population with cancer. Dr. Kalt explained that more than 426,000 persons were enrolled in epidemiologic studies in Asia, and more than 300,000 persons of Asian ethnicity were enrolled in studies in the United States, principally in Hawaii and California. Some of these studies were performed to shed light on the difference between genetics and environment by following these populations as they moved to the United States and examining changes in incidence and prevalence of various cancers. Further statistical analysis showed that when foreign Asian populations were removed from the aggregate totals, white subjects continued to be underrepresented, but their relative number with respect to the total study population increased. Hispanic and black populations remained overrepresented. Dr. Kalt noted that accruing Native American subjects to trials has in general been a difficult task, but the Special Populations Network is currently providing funds to assist investigators in recruiting individuals of this ethnicity. Dr. Kalt displayed slides depicting absolute and relative enrollment numbers by race/ethnicity for prevention and cancer control and treatment trials and for Cooperative Group treatment trials. Blacks were slightly underrepresented in the prevention and cancer control and treatment trials, but otherwise, Dr. Kalt said, NCI was doing very well in maintaining balanced populations of subjects for valid analysis. Dr. Kalt concluded his presentation by stating that gender distribution in clinical trials is well balanced overall.

Questions and Answers

Dr. Sandra Millon-Underwood, Associate Professor, University of Wisconsin-Milwaukee School of Nursing, asked whether aggregate accrual data by race/ethnicity and gender were available on prevention and screening trials. Dr. Kalt replied that the data could be made available, but the definitions of the types of trials—e.g., observational, interventional study—may not be completely uniform. Dr. Millon-Underwood requested supplementing future reports on "Accrual of Women and Minorities into NCI Clinical Trials" with more aggregate data for nontreatment trials. Dr. Millon-Underwood also asked whether data were available on the enrollment of children into clinical trials Dr. Kalt responded that, for treatment trials, these data were primarily available through the NCI-funded Clinical Cooperative Groups, which have enrolled 60 to 70 percent of the entire U.S. pediatric population with cancer.

Dr. Millon-Underwood asked which NCI office was responsible for collecting and monitoring accrual data. Dr. Kalt indicated that the newly created National Center for Research in Minority Health and Health Disparities, to be headed by Dr. Harold Freeman, houses these activities. Dr. Kalt requested a motion from the Board to certify NCI compliance and to accept the biennial report on "Accrual of Women and Minorities to NCI Phase III Clinical Trials." The motion was made, seconded, and approved.

VII. NEW BUSINESS I—DR. PHILLIP SHARP

Dr. Sharp asked for the Board's permission to write a letter to Congressional leaders expressing the Board's appreciation for the recent 13 percent increase in the NCI budget for FY 2001. The request was unanimously approved.

VIII. PROTECTION OF HUMAN SUBJECTS RESEARCH UPDATE—DRS. GREG KOSKI AND RONALD GELLER

Overview of the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP). Dr. Greg Koski, Director, OHRP, DHHS, pointed out that human research has changed radically since the current system of protections was built 30 years ago. Biomedical research has new tools and poses new risks to individuals and communities. The existing system has been focused on institutional review boards (IRBs) as the key element for protection of human research subjects, and, according to the Office of the Inspector General, IRBs are being asked to review too much too quickly with too few resources and too little expertise. Dr. Koski indicated that his office is looking for ways to take advantage of the structure and resources that currently exist and to apply those to a process that will meet the needs of the research community.

The recently established OHRP grew out of the former Office for the Protection of Research Risks that was based at NIH. OHRP is working to achieve four goals in the design of a new framework: simplicity, uniformity, efficiency, and effectiveness. Moreover, the process of protection of human subjects cannot be entrusted solely to government. The research community must move toward a new environment of shared responsibilities and collaboration with the private sector and make use of proven tools of effective management, such as individual certification programs and accreditation programs for human subject protection, to complement the regulatory role of Government. OHRP is a relatively new office, but it has already reached some important milestones: (1) a unified Federal registration system for all IRBs, which will result in a database that contains information of where IRBs are, how they are constituted, what kinds of work they are reviewing, and what volume of work they handle; (2) a simplified assurance process that allows all Federal agencies to recognize a single assurance and avoid redundancy. The assurance guarantees that any entity that receives Federal research funds will follow Federal rules for protection of human subjects. Dr. Koski stated that this assurance process, in concert with private voluntary accreditation and certification programs, will result in a rapid move to a system that is far more effective than the existing one. He also said that such a new system would allow multiple institutions, having attained the assurance of following Federal rules, to rely on a single IRB in multisite research rather than on multiple IRBs. With these efforts toward simplification, Dr. Koski said he could redeploy the resources of his office from the laborious process of negotiating assurances to supporting quality improvement.

Dr. Koski described the committees that are helping OHRP achieve its goals. These include: (1) the Research Oversight Policy Coordinating Committee, consisting of representatives from other DHHS agencies engaged in human research with the purpose of achieving uniform policies within the Department; (2) the Human Subjects Research Subcommittee (HSRS) of the Committee on Science, part of the National Science and Technology Council of the Office of Science and Technology Policy at the White House, which can help develop an integrated system across the entire Federal Government; and (3) the National Human Research Protections Advisory Committee, a new committee that will get input and advice from Government agencies as well as the public on critical policy questions. Dr. Koski noted that the IOM has been engaged in a three-part study of the human research protection process. The charge is to: (1) develop standards for accreditation of human research protection programs; (2) assess OHRP's activities to determine whether the Office is addressing the critical issues or whether midcourse corrections are needed; and (3) identify a set of objective measurement techniques for the effectiveness of the human research protection process.

Questions and Answers

Dr. Klausner asked for further comments on the IOM's accreditation criteria. Dr. Koski replied that the standards must be established by a group with sufficient influence in the community so that these will be widely accepted. Dr. Koski said that OHRP will also review the standards. Two private organizations have expressed interest in being accrediting bodies: the National Council for Quality Assurance and the Association of Human Research Protection Programs. The first version of the standards is to be available April 1, 2001, and will undergo a period of testing for reliability and validity.

Dr. Sharp asked about possible rules addressing conflicts of interest related to human research. Dr. Koski agreed that even the appearance of a conflict of interest of financial nature can be damaging to the research, and, in the worst case, actually undermine the integrity of the research. Dr. Koski added that a conference was convened in August 2000 with representatives of the public, the pharmaceutical industry, and academic institutions to discuss this issue, and a summary of the discussion has been posted on OHRP's Web site as draft interim guidance for public comment. Comments will be reviewed by the National Human Research Protections Advisory Committee, and Dr. Koski speculated that additional guidance or even new regulations might be issued if necessary.

Dr. Klausner asked Dr. Koski for comment on the implications of the proposed privacy and confidentiality regulations for OHRP's concerns. Dr. Koski said the regulations, which are still undergoing public comment, will not take effect for 2 years. However, he said he doubted the regulations would be onerous in the research community because the regulations already provide for appropriate waivers of informed consent for matching the protections to the level of risk. Privacy regulations should not cripple valuable research, so it is necessary to find the right balance. Dr. Koski indicated that the research community must care enough about its subjects to put their interests first to build a foundation of trust.

NIH Oversight of Research Involving Human Subjects. Dr. Ronald Geller, Director, Office of Extramural Programs (OEP), NIH, said that his office began reexamining its policies, practices and procedures in response to Dr. Koski's redefining of the roles and responsibilities of OHRP. Dr. Geller explained that the OPRR, OHPR's predecessor, was responsible for approving and dealing with all assurances and for handling the NIH peer-review coding system associated with human subjects. The office operated on a grant-by-grant or contract-by-contract basis. Dr. Geller indicated that the system involved an enormous duplication of effort, justifiable only by the argument that some procedures had always been done in a certain way. When OPRR became OHPR, it no longer had direct responsibility for handling NIH awards. Instead, each agency had responsibility for its own policies and procedures for protecting human subjects and was required to report to OHRP. Each agency also was required to establish a contact point, procedures for handling restricted awards, and a monitoring plan. OEP became the contact point for NIH and acquired new policy responsibilities: (1) developing an improved coding system that would track the number of projects involving human subjects and issues of concern arising during the review process; (2) issuing policies for awards of grants and contracts involving human subjects; (3) reviewing fundable projects for which concerns about human subjects research had been raised and approving an appropriate resolution; and (4) developing a monitoring plan for research involving human subjects that would meet the requirements of OHRP.

Dr. Geller noted that a small group of NIH staff met frequently with OHRP staff to review virtually every step of the NIH process, with the goal of developing procedures consistent with OHRP standards and to enable individual institutes to take on the responsibility and accountability for ensuring that human subjects concerns were addressed, and for improving the timeliness of making awards. Dr. Geller said that the OEP discovered that no NIH-wide committee existed to deal with these issues, so a committee was established to put together new procedures. In developing a new coding scheme, the committee found that the definition of a "human subjects concern" was overly broad, ranging from a request for clarification to a serious concern. A new definition was established: "Any actual or potential unacceptable risk, or inadequate protection against risk, to human subjects." This definition was developed for reviewers, scientific research administrators, and program officials to use in evaluating research proposals. The new definition does not include issues related to assurances or IRB certifications. The goal of these new procedures is to simplify the process by giving the institutes greater responsibility for getting answers to concerns and resolving issues more quickly. Dr. Geller concluded by listing other initiatives of OEP, such as consolidating the Human Subjects section of the 398 application form and providing continuing education on human subjects that is tailored to the responsibilities of scientific review administrators, program officials, grants managers, and contracting officers.

Questions and Answers

Dr. Robert Wittes, Deputy Director for Extramural Science, NCI, said that under the current system, investigators' research involving human subjects is governed not only by regulations but also by interim statements made by various agencies of the Government, usually in reaction to a crisis. These statements have come from NIH, the Food and Drug Administration (FDA), OPRR, and other agencies. Dr. Wittes stated that the Government is not speaking with one voice, and the outcome is not conducive to either good protection of human subjects or the free conduct of research within societal limits. He praised Dr. Koski's efforts to seek interagency cooperation. Dr. Koski responded that the HSRS plans to convene a task force that will include a broad cross-section constituency from organizations involved with human subjects research, investigators, and Government representatives. The group will be asked to brainstorm and produce a list of initiatives that could be initiated immediately to achieve the goals of simplicity, uniformity, efficiency, and effectiveness.

Ms. Mary McCabe, Director, Office of Education and Special Initiatives, NCI, asked Dr. Koski to comment on efforts to coordinate regulations and rules between FDA and OHRP. Dr. Koski cited adverse event reporting as an example of a regulation in need of coordination. HSRS has formed a committee to look into harmonization of adverse event reporting requirements.

Dr. Li said that a major problem with Federal rules occurs when the interpretation of rules changes. Investigators who want to act in an ethical manner, he said, find themselves with a human subjects concern involving what was previously standard practice. As an example, he cited an article that suggested that previously collected data on names of family members might now be considered unethical. Dr. Koski agreed that rules need to be applied in a more thoughtful and uniform manner. With respect to confidentiality issues and family members, he drew the distinction between medicine and research. In medicine, he said, taking family histories is done because it is critical to patient care. In research, the goal is to create generalizable knowledge, and investigators must develop strategies to obtain the information needed for meaningful research and at the same time maintain respect for the individual's need for privacy. Physicians routinely ask patients about family members' causes of death, he pointed out, and

such information is widely accepted as part of the medical record. However, when questions concern genetic data or deviant behavior, a fundamental issue of privacy is raised. People have certain expectations that such sensitive information will not be shared with anyone else. Dr. Koski said that protections need to be put in place that are commensurate with the risks.

Dr. Norton suggested that "expeditious" be added to Dr. Koski's four goals of simplicity, uniformity, efficiency, and effectiveness. As an example, he pointed to the time delays involved in getting a multi-institutional trial through all the various IRBs. Dr. Koski replied that the model his office has put in place has already addressed that particular issue. One way of streamlining the IRB process is for academic organizations to come together and create a network so that one IRB will review one multisite trial, and another IRB will review another. An alternative model being explored at NCI involves relying on a centralized IRB that would be national in composition, structure, and placement for the core review and approval of all clinical trial protocols. This IRB would be part of a broader system that would include a local apparatus to monitor the actual implementation of the trial. Having a single IRB review a 30-center trial would cut red tape enormously. Dr. Koski predicted a more professionalized structure for research review programs. In the private sector, he said, private professional IRBs with enormous expertise are used, and they are better positioned to maintain a relationship free from financial or institutional pressure than academic IRBs. Dr. Koski closed by telling Board members that the success of the process depends on all sectors working together.

IX. NATIONAL CANCER POLICY BOARD REPORT: ENHANCING DATA SYSTEMS FOR QUALITY CANCER CARE—DRS. ROGER HERDMAN AND MARIA HEWITT

National Cancer Policy Board. Dr. Roger Herdman, Director, National Cancer Policy Board (NCPB), IOM, NAS, gave the NCAB a brief description of the Board and the reports it has issued during its first 3 years of existence. These include: *Ensuring Quality Cancer Care* (1999), *Enhancing Data Systems to Improve the Quality of Cancer Care* (2000), *Interpreting the Volume-Outcome Relationship in the Context of Health Care Quality* (2000), *Taking Action to Reduce Tobacco Use* (1998), and *State Programs Can Reduce Tobacco Use* (2000). Reports in preparation include *Ensuring Quality Palliative Care for Cancer Patients from Diagnosis to the End of Life*, which is planned for publication in the late spring or early summer of 2001; and *Describing Death in America: What We Need to Know*, which will examine the availability of data on patients receiving palliative care and the potential to improve those data resources. A project on State cancer control and State cancer plans is in the evaluation stage. Dr. Herdman directed the NCAB's attention to background materials concerning the findings and recommendations in *Ensuring Quality Cancer Care*. Problems in delivering quality care, he said, are serious and pervasive. However, several of the report's recommendations have been taken up by the National Dialogue on Cancer, and a Senate committee is considering legislation to expand cervical and breast cancer screening programs, an initiative that addresses one of the Board's identified problem areas, the underuse of screening for early cancer detection.

Enhancing Data Systems to Improve the Quality of Cancer Care. Dr. Maria Hewitt, Senior Program Officer, NCPB, IOM, NAS, said that the Board, in preparing for the report *Ensuring Quality Cancer Care*, had difficulty in judging the quality of care across the United States because of a lack of recent data. Moreover, information was limited on the care experiences across geographic areas and in different care settings. In response to these problems, the NCPB held a workshop in October 1999 specifically to address data issues. The NCPB drafted recommendations and a report, based in part on the

workshop proceedings, and the Board held an open forum for representatives from data systems, health care systems, and health services research to review the recommendations and provide comments. Dr. Hewitt reviewed the major findings and policy recommendations of the Board that are summarized in the report, entitled *Enhancing Data Systems to Improve the Quality of Cancer Care.* The NCPB identified three uses of data to improve quality of care: (1) performance data for health care systems can be used internally for quality improvement or by health care purchasers to exert leverage on providers; (2) data can be used for national monitoring to help gauge the status of cancer care and to provide benchmarks for health systems; and (3) data can be used for health services research to identify the underpinnings of quality problems. An ideal data system, Dr. Hewitt said, would include information on recently diagnosed patients, care settings representative of contemporary practice, wide national and regional representation so findings could be generalized, and sufficient detail on processes of care known to be linked to favorable outcomes. The NCPB identified five ingredients necessary to implementing an ideal data system: (1) comprehensive and coordinated national data systems; (2) leadership within the cancer care community; (3) cooperation among groups providing cancer data; (4) integration with ongoing efforts in quality improvement; and (5) application of new information technologies. Dr. Hewitt said that cancer is one of the few chronic diseases for which there is an organized registration process in place. She cited the CDC's National Program of Cancer Registries, now in 45 States; NCI's Surveillance Epidemiology and End Results Program (SEER), which has just been expanded; and the National Cancer Data Base of the American Cancer Society and the American College of Surgeons. She said that linking these data sources to administrative data—for example, linking SEER data to Medicare claims—has allowed health services researchers to assess a number of quality-related questions. Another strategy in use is special studies of cases sampled from registries.

The NCPB recommended that a committee be appointed to develop a single core set of cancer care quality measures based on the best available evidence. Such measures should span the full spectrum of an individual's care. Dr. Hewitt said that there are many examples of quality measures in the health services research literature, and some that the NCPB reviewed in *Ensuring Quality Cancer Care* included documentation of staging information, presentation of treatment options to patients, and appropriate use of adjuvant therapies. Another Board recommendation was to increase Federal support for CDC's National Program of Cancer Registries. Only 19 States meet standards for completeness, accuracy, and timely reporting of incident cancer cases, she said, and additional funding might help bring other States up to the standard. Dr. Hewitt indicated that another important need is for increased technical assistance to States for quality studies. Some States, and she named Colorado as an example, have already begun to use cancer registry data to assess quality. The Board also encouraged increased private support for the National Cancer Data Base. In the area of research and training, Dr. Hewitt noted that Board recommendations included more Federal research on new mechanisms to organize and finance data collection for cancer care quality studies; establishment of public-private partnerships to develop technologies to improve quality and timeliness of clinical data; and expanded support for training and health services research. In closing, Dr. Hewitt indicated that the NCPB plans to monitor the implementation of its recommendations.

Questions and Answers

Dr. Klausner asked Dr. Robert Hiatt, Deputy Director, Division of Cancer Control and Population Sciences (DCCPS), NCI, and Dr. Joe Lipscomb, Chief, Outcomes Research Branch, DCCPS, to comment on some of the issues raised in the NCPB report. Dr. Hiatt said that NCPB's recommendations are

consistent with the Quality of Care initiative of his Division. He added that better types of measurement—not only process and quality measurement, but also outcomes measurement—were needed. Outcomes measurement would include not only survival and mortality, but also those measures important to cancer patients: quality of life, performance measures, impact on family, and financial costs. The second measurement issue, according to Dr. Hiatt, involves establishing guidelines for agreed-upon process and quality measures. This issue is the same as that in the first recommendation from the NCPB, but DCCPS believes that a public-private committee, such as the National Quality Forum, would be more effective in bringing together interests from the Government, industry, third-party payers, professional organizations, and accrediting organizations than would a DHHS committee.

Dr. Hiatt described the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), which he said was an empiric base to establish the reliability of a link between findings from following up patients over long periods of time and quality measures and outcomes. Another key element is the role of the Quality of Care Cancer Committee in selecting Federal projects involving interagency collaboration. Two projects, one with the Department of Veterans Affairs (VA) and one with the Health Care Financing Administration (HCFA), focus on colorectal cancer. The Committee is working with the Health Resources and Services Administration (HRSA) to improve diagnosis, referral, and treatment within HRSA clinics. Another project, in collaboration with the FDA, examines relative benefits of symptom measures versus quality-of-life measures following drug treatment.

Dr. Howard Koh, Commissioner, Massachusetts Department of Public Health, asked whether any overall summary measure for quantifying quality of cancer care is currently available. Dr. Hiatt replied that there was no such measure currently available, and that different sites of cancer, different stages of cancer, and different applications all influence the appropriate quality measure. He said that ultimately arriving at some 20 measures would be good. Dr. Sharp advised NCAB members to review the NCPB recommendations carefully, and he also asked for clarification about the inclusion of prevention in the definition of quality of cancer care. Dr. Hewitt said that the report on data systems focused on care, but the Board's current work involves prevention and early detection as part of the quality of care. In response to Dr. Sharp's inquiry about the amount of NCI's budget assigned for research programs related to quality of care, Dr. Lipscomb replied that it is $20.5 million.

Dr. Harold Freeman, Chair, President's Cancer Panel, inquired as to whether the studies of measurements of quality of care took into account the fact that many people, particularly those lacking health insurance, have difficulty getting access to care. Dr. Hewitt responded that the initial report on quality of care dealt with access issues but the report on data systems focused on health care systems measures rather than population-based measures. Dr. Herdman added that the IOM is mounting a major effort to explore problems of the uninsured. Dr. Hiatt cited CanCORS as a population-based initiative that tracks people who are uninsured, as well as those insured under different modalities. Dr. Freeman pointed out that existing registries and databases do not deal with quality issues, and he asked whether the NCPB thought it was best to work with systems that already exist or if the NCPB hoped to create a new system to collect quality data. Dr. Hewitt answered that the Board had decided to take an incremental approach by working with available data systems, with the hope that advances in information technology, computer-based records, Internet systems, and vertically integrated health care systems will materialize. Dr. Herdman said that the NCPB's reports made it clear that quality data need to be collected, and a core set of quality indicators could be part of the design of the required data systems. He said that adding such elements to national data collection efforts would receive wide acceptance.

X. ANNUAL DELEGATIONS OF AUTHORITY—DR. MARVIN KALT AND MS. MARYANN GUERRA

Delegations of Authority. Dr. Kalt briefly reviewed the delegations of authority to be requested annually from the NCAB, as stated in the Public Health Service Act. He explained that the agreement with the Board in regard to these delegations permits the NCI to accomplish the administrative tasks needed to ensure that awards and administrative requests are processed in a timely manner. Delegation A allows the Director, NCI, to obtain the services of up to 151 experts or consultants who have scientific or professional qualifications to assist in accomplishing the mission of the Institute. Dr. Kalt noted that hiring will be subject to the hiring freeze currently in place. Delegation B grants authority to the Director and the Institute to appoint one or more advisory committees, such as the Director's Consumer Liaison Group; the Advisory Committee to the Director, NCI; and the Boards of Scientific Advisors and Scientific Counselors, to advise the Director with respect to his or her functions. Dr. Kalt explained that the second part of the annual delegations of authority was embodied in the "Statement of Understanding With the NCI Staff on Operating Principles in Extramural Awards." The Statement addresses: (1) extramural awards that the NCI is empowered to make without concurrence of the NCAB (e.g., scored applications with recommended direct costs of $50,000 or less); (2) provisions for decreasing the number of summary statements included in the Board Books (e.g., removal of applications scoring over the 50th percentile or raw-scored applications with scores over 250); (3) principles for conducting a process of expedited concurrence for R01 and R21applications that fall within NCI paylines for the year and have no concerns noted that would represent an administrative bar to award (e.g., human subjects, animal welfare); and (4) permission to allow NCI staff to negotiate appropriate adjustments—such as supplementation of grants within the proposed scope of work, minor administrative changes in costs or time, or changes in institution or principal investigator—in terms and conditions of grant and cooperative agreement awards recommended by the Board. Dr. Kalt reminded the Board that members now have electronic access to any summary statement they wish to peruse. Dr. Kalt said that the expedited concurrence process had been successful, particularly in the beginning of FY 2001, when the Institute had no appropriation. For applications well within the payline, the Institute sent out notices of the intent to pay even when funds could not be released, enabling applicants to plan for the award. A motion was made to approve Delegations A and B as stated in the Public Health Service Act and the operating principles relating to extramural awards included in the statement of the understanding. The motion was seconded and unanimously approved.

In discussion, Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, requested consolidating into periodic (e.g., weekly) e-mail messages information on grant applications selected for electronic expedited concurrence rather than submitting more frequent messages with information on individual applications.

Summary Description of NCI Fellowship Programs. Ms. MaryAnn Guerra, Deputy Director for Management, Office of Management (OM), NCI, said that NCI's training fellowships programs required NCAB approval under the Public Health Service Act. Trainees constitute a large proportion of NCI's human resource count. In 2000, trainees accounted for nearly 29 percent of the workforce, with a historical average of about 30 percent. In 1998, NCI consolidated all training programs into the Cancer Research Training Award (CRTA) program. Ms. Guerra explained that foreign fellows, whose numbers are increasing significantly among postdoctoral fellows, are appointed under NIH authority, but they receive the same stipend levels as domestic fellows under CRTA, thus maintaining pay equity. In FY

2000, foreign fellows accounted for 61 percent of basic science fellows. Ms. Guerra explained that when CRTA was established, adjustments to stipend levels resulted in an 8 percent increase over the previous year's obligations. In 2000, NCI's OM conducted a biennial review to ensure that NCI's stipend levels were comparable to the external community's and to those of the National Research Service Awards (NRSA). Local cost-of-living issues also needed to be taken into account. The result was an increase in CRTA funds of about $5 million, or 17 percent. The OM staff compared NCI stipend levels with those of NIH and NRSA, which recently were increased by 6 and 5 percent, respectively. OM found that, with no further increase, CRTA stipends are within the range of NIH and NRSA fellowship programs. The OM is continuing its benchmarking to compare CRTA stipends with outside fellowships. Ms. Guerra noted that one difference between the CRTA fellowships and outside fellowships is that NCI allows no supplemental funds. The CRTA program provides for divisions within NCI to maintain their own dedicated fellowships. The Division of Cancer Epidemiology and Genetics has four fellowships: cancer epidemiology and biostatistics, genetic epidemiology, molecular epidemiology, and radiation epidemiology. There are also fellowships for cancer prevention, health communications, and technology transfer. Ms. Guerra said that a Fellowship Office was recently created within NCI to improve recruitment, career development, and mentoring of fellows, which the NCAB had been encouraging. She added that a Recruitment Office has also been established within the Office of Employment Programs and the Diversity Office. In closing, Ms. Guerra stated that the intramural divisions are the primary leads in recruitment, so division deans have been appointed to develop relationships between the Fellowship Office and the Recruitment Office.

Questions and Answers

Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Center, asked whether there was a breakdown of the number of foreign fellows with respect to country of origin and field of study. Ms. Guerra replied that she could send him that information. Dr. Amelie Ramirez, Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, pointed out that one of Ms. Guerra's slides presented information on race and national origin, but the information on one group appeared to be collapsed. Ms. Guerra responded that the group in question—slightly more than half of the fellows—was made up of people who did not disclose information on their race and national origin. Such information can be difficult to get, she said, because disclosure is voluntary. Dr. Ramirez also asked if recruitment efforts focused more on domestic versus foreign fellows, and Ms. Guerra replied that NCI was actively recruiting domestic fellows. She pointed out that in universities, the proportion of foreign fellows exceeds 50 percent, so NCI's program reflects a national trend. Dr. Elmer E. Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, asked whether NCI had fellowships sponsored by outside organizations. Ms. Guerra said that NCI had the ability to bring on as special volunteers fellows who are supported through outside institutions. A number of individuals are at NCI through outside fellowships, she said, and she would find out how many there were. Dr. Huerta said his organization would like to sponsor fellowships, and Dr. Klausner said that NCI encourages such relationships but also advises Principal Investigators to look for outside support for postdoctoral fellows.

Dr. Sharp concluded the session by asking for a motion to continue delegating permission from the intramural education and training programs, including education and laboratory and clinical research training. The motion was made, seconded, and unanimously approved.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Dr. Sharp reminded Board members that the material furnished for review and discussion during the closed portion of the meeting is considered privileged information.

He stated that advisors and consultants serving as members of chartered advisory committees may not participate in situations wherein any violation of conflict of interest laws and regulations might occur. He indicated that responsible NCI staff would ensure that each Board member would not perform duties or render advice that might have a direct and predictable effect on the interest of any organization or institution in which he/she had a financial interest. In particular, Board members were informed that they could not participate in the evaluation of grant applications or projects for Federal funding, in which, to the member's knowledge, any of the following had a financial interest: the committee member; his/her spouse; an individual with whom the member has a close personal relationship; a dependent child, parent, partner (including close professional associates) or with an organization with whom the member or other parties named is seeking employment or serving as an officer, director, trustee, general partner, agent, attorney, consultant or contractor.

Members were instructed to exit the room if they deemed their participation in the deliberation of any matter before the board to be a real conflict or would represent the appearance of a conflict. Members were asked to sign a conflict of interest/confidentiality certification to this effect.

During the closed session of the meeting, a total of 1,434 grant applications were reviewed requesting support of $468,855,529. Funding for those 1,434 applications was recommended at a level of $456,252,855.

The closed session adjourned at 5:15 p.m..

DAY TWO – FEBRUARY 14, 2001

XI. UPDATE ON CLINICAL TRIALS—DRS. MICHAELE CHRISTIAN AND ROBERT WITTES

Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI, spoke about the size and scope of the Clinical Trials Program, gave an overview of the portfolio of investigational agents, and provided a few significant examples of approaches taken in the areas of therapeutic development, encompassing drug-based, target-based, and disease-based development. The classes of investigational drugs span a broad range and include the following: angiogenesis inhibitors, antimetabolites, antitubulin agents, cytokines, differentiators, DNA-interactive agents, gene-therapy drugs, monoclonal antibodies, mediators of targeted radiotherapy, immunotoxins, radiosensitizers/photosensitizers, and signal-transduction inhibitors. The extensive collaborations with industry provide many of these drugs, but a growing number of agents come from academia and from NCI's own intramural program. NCI's unique vantage point for drug acquisition has positive ramifications for developing combination therapies, a topic broached later on in the presentation.

Size and Scope of the Clinical Trials Program. The tremendous number of new drug targets reflects the explosion in the understanding of cancer biology. CTEP holds 157 Investigational New Drug (IND) applications across the broad range of targets. In the past year, 414 clinical trials began actively accruing patients, and 191 new trials were initiated. Accrual to large Phase III studies, however, takes a median of 4.7 years. The accrual figure has remained relatively stable over the past 3 years and is achieved primarily through the Clinical Trials Cooperative Groups. Dr. Christian noted that a gender bias is seen in the overall portfolio, with women outnumbering men 60 percent to 40 percent. However, this ratio is reversed if gender-specific diseases are excluded.

Therapeutics Development: Target-based Development. A target-based treatment focuses on disrupting particular molecular targets that differentiate cancerous cells from nonmalignant cells. In the examples of lung cancer, several targets relate to cell cycle, and each identified target can have numerous agents that affect it. An added complexity is the fear that numerous molecular pathways may contribute to the final cell response and phenotype. The fundamental knowledge gained by blocking a particular pathway contributes not only to the understanding of cancer, but also, in some cases, to a positive clinical outcome. The Astro Zeneca compound ZD1839 is such an example, effective in blocking the epidermal growth factor receptor (EGFR) signaling pathway. Many epithelial cancers express high levels of EGFR and will be important potential candidates for targeted inhibition in clinical trials. The endpoints in such trials can be tumor regression, indicating that the agents have cytotoxic effects; or the absence of progression, indicating that the treatment compounds have cytostatic activity. Overall, target-based agents contribute to an understanding of the biology of cancer and, individually, highlight key molecular pathways within the cancerous cell.

Therapeutics Development: Agent/drug-based Development. Therapeutics development can also be agent- or drug-based. The drug STI571, a tyrosine kinase inhibitor, was initially developed because of its activity against chronic myelogenous leukemia and was subsequently found to affect other targets such as c-kit and platelet-derived growth factor (PDGF) receptors. Agents with numerous targets may be efficacious against numerous cancers, and combinations of drug- and target-based therapies may

be important to investigate as avenues of treatment. However, in the case of STI571, specific clinical efficacy is not always predicable; STI571 has striking activity against rare gastrointestinal stromal tumors, presumably because of this type of tumor's characteristic c-kit mutation. STI571 is one of the first examples of a specific molecular target agent with significant activity in a solid tumor. Because of this property, a particularly exciting aspect of the development plan for STI571 is being able to correlate clinical procedures and outcomes with laboratory discoveries. As more is understood about the signaling pathways within cells, and as an increased number of agents are characterized that inhibit signaling at different points, combination studies will have the potential to enhance the effectiveness of cancer drugs. A new direction undertaken by CTEP is to begin combination studies early in the development of cancer agents. The NCI is in a unique position to investigate combinations involving multiple compounds. Dr. Christian highlighted a number of agents with promising Phase I antitumor activity.

Therapeutics Development: Disease-based Development. Determining the appropriate treatment of cancer requires assessment of the disease stage. Different stages or subtypes of a particular cancer respond to different clinical therapies. Breast cancer was used as an example to highlight the questions that can be asked when comparing different treatments at Clinical Stage 5. The goal of combination therapy is to combine appropriate therapeutic modules to improve outcome in this group of patients and eventually introduce new treatments to earlier-stage disease. Other treatment advances from large Phase III trials in the Cooperative Groups have impacted patients with gastric cancer. A comparison of surgery with and without adjuvant therapy has impacted treatment, and the cure rate is expected to improve by approximately 1,000 patients per year. Likewise, data on the inclusion of older individuals in clinical trials have indicated that age does not decrease the effectiveness of chemotherapy if the patients have adequate performance status. Finally, in renal cell carcinoma, a Phase III trial showed that nephrectomy plus adjuvant therapy with interferon improved survival time when compared with interferon treatment alone. These important advances in knowledge gained from Phase III trials directly impact disease treatment and stimulate additional research into effective therapy.

External Collaborations. Dr. Christian noted that, as the development of therapeutics becomes increasingly complex, the need arises for multidisciplinary research teams to evaluate ideas on novel treatments. Dr. Christian cited the establishment of new working groups as a means to foster the exchange of ideas, address such issues as long-range planning, and evaluate assays and tools available for early clinical trials. Four such working groups have been initiated, addressing issues in the areas of clinical trial design, signal transduction, immunotherapy, and angiogenesis. Dr. Christian also mentioned the development of interdisciplinary research teams for molecular target assessment. NCI funds collaborations between laboratories of basic and clinical research. Ultimately, both scientists and patients will benefit from the newly developed assays and tools. In closing, Dr. Christian provided oversight into the kinds of agents in the CTEP portfolio and in the development of these agents. She summarized the prospects for developing and testing combinations of agents and predicted an increasing speed of treatment development through the Clinical Trials Program.

Questions and Answers

Dr. Norton inquired about the composition of interdisciplinary teams and whether there was much overlap with or interplay between intramural NCI investigators. Dr. Christian replied that the program for interdisciplinary research teams for molecular target assessment is a grants program, and the teams are composed of members within an extramural institution or between extramural institutions. Dr. Christian

did not recall intramural participation in these teams; however, the Immunology Working Group, for example, capitalizes on resources that exist both intramurally and extramurally. A question by Dr. Sharp focused on the type of therapeutic agents under investigation by CTEP. Dr. Christian reflected that in more recent years, the portfolio has moved away from cytotoxics to more targeted therapies. The amount of money invested in novel agents versus cytotoxics, a question asked by Dr. Sharp, was answered by Dr. Wittes as being roughly proportional to the agent distribution, disregarding the agents from the Intramural Program where individual INDs are filed.

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, MD Anderson Cancer Center, asked how CTEP planned to enhance participation of older patients in trials. Dr. Christian noted that protocols restricting age are not accepted. Dr. Wittes pointed out that the new generation of therapeutics is significantly more selective and therefore less toxic than earlier agents. As physicians become aware of these improvements, the barrier to treating elderly patients will dissolve. Dr. Klausner requested more information about combination therapies and, specifically, asked Dr. Christian and Dr. Richard Pazdur, Director, Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), Office of Review Management (ORM), FDA, to speak to potential problems and future plans. Dr. Christian remarked that potential combination therapies often involve agents in development by industry, and that intellectual property and other issues create significant hurdles. Dr. Pazdur agreed and mentioned that the effectiveness of individual agents has to be researched prior to regulatory approval for commercialization. Dr. Wittes felt that encouragement to develop an agent in combination with other drugs must be provided by the FDA before companies will be willing to risk their particular agents. Dr. Pazdur discussed time-to-progression as a surrogate endpoint, rather than patient survival times. Often, differences in time-to-progression are negligible among different therapeutic agents, but the significant advantage to using an alternative to survival as an endpoint is the reduced time required to complete the studies. Dr. Christian responded that the NCI will be holding monthly meetings with the FDA to resolve this kind of issue. Development of the STI571 agent, in particular, will provide a fertile area for discussions with the FDA about rapidly reached endpoints and combination therapies. Drs. Klausner and Sharp both expressed excitement about this test case. Dr. Huerta questioned the percentage of minorities that will be accrued in clinical trials this year. Dr. Christian asserted that this problem is being addressed by actively involving minority institutions.

XII. SUBCOMMITTEE REPORTS

Subcommittee on Communications. Dr. Love presented the Subcommittee on Communications' written report for Board acceptance. The Subcommittee heard an update from Dr. Susan Sieber, Director, NCI Office of Communications (OC), that detailed the five major programs comprising the OC. Members also discussed the NCI Office of Education and Special Initiatives' programs to increase understanding of access to clinical trials and the Board's role in disseminating information about the Executive Memorandum from President Clinton regarding the HCFA Medicare National Coverage Decision for Clinical Trials. Subcommittee members indicated that they would like to revisit the National Coverage Decision at a future meeting. A final topic for discussion was the Consumer Advocates in Research and Related Activities (CARRA) program and ways to incorporate advocates into NCI. The Subcommittee asked to meet with OC staff who are working on this initiative during their next meeting. The Subcommittee made plans to meet at the next NCAB meeting. Subcommittee members asked that OC Associate Directors produce a handout with biosketches and plans for the future. They also agreed to meet jointly with the Subcommittee on Planning and Budget.

Subcommittee on Planning and Budget. Ms. Ellen Stovall, Executive Director, National Coalition for Cancer Survivorship, presented the Subcommittee on Planning and Budget's written report for Board acceptance. The Subcommittee discussed a proposed plan for soliciting ideas for the new cycle of Extraordinary Opportunities. The goal is to obtain input from groups not normally included in the process. One suggestion was to solicit ideas from nonmedical professional associations such as those representing the computer science and communications technology fields. The Subcommittee also reviewed a brochure entitled *Help Us Imagine and Build the Future of Cancer Research*, designed to solicit input on Extraordinary Opportunities, which the Subcommittee heartily endorsed. The Subcommittee plans to meet at the next NCAB meeting jointly with the Subcommittee on Communications. A discussion ensued among Board members on NCI's processing of public input on Extraordinary Opportunities and the importance of responsiveness to such communications. Dr. Sharp suggested writing an acknowledgment on the Extraordinary Opportunities for Investment form thanking respondents in advance for participating in the program and indicating that there will be no reply letter.

A motion was made to accept the Subcommittee reports as written. The motion was seconded and unanimously approved.

In response to request by Dr. Ramirez, Dr. Hiatt briefly reported on the working lunch presentation on Interagency Cooperation in Cancer Control. He indicated that the session represented an opportunity to display some of the activities that the Division of Cancer Control and Population Sciences has undertaken in collaboration with other agencies to move research findings into practice. The interagency collaboration spans a broad spectrum of activities related to cancer control and surveillance, tobacco, nutrition, and genetics.

XIII. NEW BUSINESS II—DR. PHILLIP SHARP

There were no items for discussion under New Business II.

XIV. PROGRESS REVIEW GROUP REPORT: PANCREATIC CANCER—DRS. SCOTT KERN AND MARGARET TEMPERO

To present the report of the Pancreatic Cancer Progress Review Group (PRG) for NCAB consideration, Dr. Klausner introduced the co-chairs: Dr. Scott Kern, Associate Professor, Department of Oncology, the Johns Hopkins University; and Dr. Margaret Tempero, Deputy Director, Comprehensive Cancer Center, University of California San Francisco. He thanked them, as well as Dr. Barbara Conley, Executive Director of the PRG, and other PRG members and NCI staff for their contributions to the understanding of pancreatic cancer. Dr. Kern outlined the charge for the PRG on pancreatic cancer: (1) to identify and prioritize research opportunities and needs in order to advance medical progress; (2) to define the scientific resources needed to address these opportunities and needs; (3) to compare and contrast priorities with the current NCI research portfolio; and (4) to prepare a written report that includes findings and recommendations. Dr. Kern stated that pancreatic cancer is the fourth most common cause of cancer death in both men and women. To illustrate the lethality of the disease, Dr. Kern noted that 29,200 new cases of pancreatic cancer are expected this year, along with 28,900 deaths from the disease. Only 4 percent of patients remain alive 5 years after diagnosis. He said that funding for the disease is limited. NCI estimated funding for pancreatic cancer to be $17 million in 1999. It is insufficiently studied in both

the laboratory and the clinic, and there are very few investigators who focus exclusively on pancreatic cancer. Dr. Kern outlined challenges and opportunities in the following four areas:

Biology. Dr. Kern said that the challenges confronting scientists are daunting. The basic biology regarding differentiation and development of normal pancreatic cells is poorly understood. Moreover, the molecular events in tumorigenesis are inadequately defined, so there is no definitive model of the cancer's invasiveness and aggressiveness. The host-tumor interactions are more pronounced in pancreatic cancer than in any other type of cancer, to the extent that the morbidity of the patients is out of proportion to the tumor bulk compared with the tumor bulk in most other common solid tumors. The nature of the pancreatic cancer resistance to conventional treatments is also poorly understood. Dr. Kern indicated that there are a number of opportunities to build on promising findings. Genetic alterations have been identified within pancreatic cancer, and in some cases they can be detected within a patient. Some germline mutations have been shown to predispose carriers to this cancer, so within a family, the reasons why some members get pancreatic cancer while others do not contract the disease can be identified. Some tumor-stromal interactions have been characterized, and these findings could serve as an opportunity for diagnosis and as a pivotal point for therapeutic interventions.

Risk/Prevention/Detection/Diagnosis. One of the most difficult challenges in treating pancreatic cancer is that the patient seldom exhibits specific symptoms until the cancer is advanced and it is too late for intervention. Solving that problem would require identifying premalignant and early malignant lesions; however, the technology to do this is not yet available. Another challenge is to identify high-risk candidates, institute preventive techniques, and place these individuals into early detection screening systems. However, the ability to detect high-risk candidates in the general population is not feasible at the present time. Four probable risk factors have been identified that could represent opportunities for action: family history, smoking, diabetes, and chronic pancreatitis. Dr. Kern noted that smoking may be associated with about one-third of all pancreatic cancers. Diabetes tends to appear in patients before the earliest recognizable symptoms of cancer, and identifying these patients may permit application of early diagnostic techniques. Patients with familial chronic pancreatitis are at higher risk of developing pancreatic cancer. Other risk factors that may apply to the general population include elevated body mass index and certain occupational exposures. There are, however, opportunities with the evolution of new technologies for molecular diagnostic approaches involving serology or analysis of pancreatic fluid.

Therapy. Dr. Kern indicated that for therapy to be effective, early diagnosis would be ideal. Most patients, however, are never identified at an early stage, and thus, therapy remains a challenge. In addition, the disease disseminates very early, providing only a small window in which to institute early therapy. The impact of current therapies is still limited, and patients are often debilitated by the host-tumor interactions. Opportunities in the therapeutic field are emerging with the gain in knowledge about the genetics and molecular biology of pancreatic cancer, which is yielding new targets. Dr. Kern explained that EGFR is overexpressed in a large number of pancreatic tumors, and perhaps in the future, tyrosine kinase inhibitors will be available for treatment of these tumors. New information on the immune system and on the mechanisms of metastasis is available, which could aid in the development of effective therapies. New technologies for facilitating the rapid testing and evaluation of new agents are under study, as are new efforts in functional imaging.

Health Services Research. Very little health services research has been focused on pancreatic cancer to date, and until early diagnosis is possible, health services research will focus on postdiagnosis

communication and care for patients who are severely ill. NCI's extensive health services research program has recently enhanced its commitment to undertake initiatives in cancer communication. Patients and their caregivers will likely provide a driving impetus for more comprehensive information.

In closing, Dr. Kern indicated that the PRG has identified scientific tools, technologies, and resources that are needed to advance the understanding of pancreatic cancer.

Creating the Agenda for Action. Dr. Tempero described the PRG process adopted for pancreatic cancer and the recommendations derived after an intense 3-day workshop. She indicated that the workshop included state-of-the-art presentations on pancreatic cancer biology, risk, detection, prevention, and therapy as well as discussions on scientific toolkits and clinical trial networks. A panel discussion assessed the health of the field, which led to three overarching recommendations for progress: (1) to develop sustained, expanded training and career development efforts in pancreatic cancer research and care; (2) to create an interdisciplinary coordinating mechanism to monitor funding patterns and identify funding deficits and opportunities in pancreatic cancer research; and (3) to establish Centers of Excellence for pancreatic cancer research and care.

Research Priorities. Dr. Tempero said that the PRG's report called for more understanding of the normal biology of the pancreas, oncogenesis, tumor-related stroma, and host-tumor interactions. In the areas of risk, prevention, and early detection, Dr. Tempero said that the research priorities were to identify genetic factors, environmental factors, and gene-environment interactions that contribute to cancer development, and to develop and evaluate approaches for early diagnosis and prevention in high-risk cohorts, such as those with a family history of the disease. The development of preclinical models for therapy is also an important research priority. Other priorities related to therapies include facilitating the development of targeted therapeutics and techniques to assess such therapies and accelerating research into supportive care. Dr. Tempero pointed out that reversing cachexia and treating pain in pancreatic cancer patients may help them live longer. Dr. Tempero noted that the PRG could find little evidence of ongoing health services research in the area of pancreatic cancer. Thus, the group worked with specialists from other areas and with patient advocacy groups to identify key issues. These issues included: identifying effective forms of health care provider communication with patients and the kinds of messages that help patients with decisionmaking; identifying manpower requirements and costs of multidisciplinary clinical trials; and determining the efficacy of current care practices and evaluating new strategies for managing treatment and end-of-life issues.

Scientific Toolkit. Dr. Tempero reiterated the need for creating scientific tools. She indicated that PRG members recognize that research has been hampered by a lack of tools, and, therefore, they recommended the development of a "scientific toolkit" with the following components: (1) tissue banks for normal and neoplastic pancreas samples; (2) relational databases containing information on normal and abnormal cells; (3) biological sampling techniques that permit analyses of minute quantities of tissue; (4) knowledge of signaling pathways that can be organized into interrelated networks to assess the outcome of alterations in pathways found in pancreatic cancer; (5) gene-based model systems that recapitulate the biology of pancreatic cancer; and (6) imaging systems to look at molecular and functional imaging to help analyze signal pathways.

The next step for the PRG is to meet with the NCI Director to discuss a plan to ensure that the recommendations will be addressed and to determine the extent to which the recommendations are being

addressed. The group will assist NCI in tracking the process over the next several years. Dr. Tempero concluded her presentation by thanking the group convened in October and the NCI staff.

Questions and Answers

Dr. Klausner commented that a research community to work on the PRG recommendations needs to be created and invigorated. Training is also key, and once training programs are in place, more trainees will follow. He further stated that he had spoken with Dr. Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NIDDK has a strong interest in pancreatic biology and is interested in linking the work of the two Institutes on some of the interdisciplinary issues.

Dr. Royston asked whether pancreatic cancer would be an appropriate area for a SPORE. Dr. Klausner said that he had not worked with the PRG to see how the group wants to see the recommendations carried out, but he thought a SPORE-like mechanism would be very appropriate. Dr. Li said that, since the incidence of pancreatic cancer is less than those of cancers of the breast, colon, or lung, perhaps a consortium would be more effective than a SPORE grant in recruiting patients. Dr. Li also commented that investigators might want to look at early-onset cases for clues to etiology. If patients are younger than expected, he said, they are probably unusual in some way, and enough such cases might yield valuable information. Dr. Tempero replied that they had found that for families with familial excess, the average age of onset of pancreatic cancer was no different than that in sporadic cases, but she agreed that studying younger patients might yield useful information. Dr. Norton said that he thought it might not be possible to gather in a single institution a multidisciplinary team, as is called for in the SPORE model, since the disease is less common than some other types of cancer. Dr. Klausner agreed, but he said that the types of activities—for example, molecular pathology, genetics, signal transduction—are available in many institutions. The more problematic issue is having a critical mass of patients. Dr. Tempero said that another necessary component is a skilled interdisciplinary clinical care team that is integrated into the research activities.

Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital, commented that biomarkers would likely be present in pancreatic cancer because there are systemic and local effects that undoubtedly reflect abnormal gene expression. Biomarkers would be useful for early diagnosis, he said. Dr. Nienhuis asked whether the PRG had emphasized this approach. Dr. Tempero replied that the PRG had identified some biomarkers, but that there is no test that is sufficiently sensitive and highly specific that would prevent unnecessary procedures in diagnosis. They felt the emphasis ought to be on identifying high-risk cohorts and then developing a parallel effort that would address biomarkers. Dr. Kern added that high-throughput methods like gene expression profiling are still very new, but a new issue of *Cancer Research* had an article on high-throughput gene expression in pancreatic cancer that lists a number of markers that should be looked at but have only recently been named.

Dr. Ramirez asked if there was a correlation between high incidence of diabetes among African Americans and Hispanics and incidence of pancreatic cancer. Dr. Tempero replied that both the incidence of pancreatic cancer and its lethality are higher among African Americans than among other population groups. Dr. Ramirez asked whether there were plans to work with diabetes research centers, and Dr. Kern answered that the type of diabetes mainly associated with pancreatic cancer is the diabetes that appears shortly before the full clinical manifestation of the disease. Once screening technologies are available,

however, integrating diabetes patients into a screening risk-assessment program for pancreatic cancer might be useful.

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics, NCI, said that recent studies have suggested that longstanding diabetes can increase the risk of pancreatic cancer, and that obesity appears to be an independent risk factor. He said that linking pancreatic cancer research and diabetes research is a good idea. Dr. Tempero said that a factor produced by adenocarcinoma cells increases amylin production by islets. This in turn causes insulin resistance, and therefore, hyperglycemia. However, after resection, sometimes the diabetes resolves. Thus it appears that hyperglycemia is related to the actual disease process.

Dr. Huerta asked if efforts had been made to understand why young researchers seem to lack interest in pancreatic cancer. Training programs and research opportunities, he said, may not be successful unless the reasons for the lack of interest are explored. Dr. Tempero acknowledged what she called "therapeutic nihilism," an unwillingness to refer patients to other Centers and clinical trials because of the sense that nothing good will happen. However, she said investigators in the field are having an impact, and it is worthwhile for patients to access clinical trials.

XV. HIGH VISIBILITY STUDIES OF ENVIRONMENTAL RISKS FOR CANCER: RISKS ASSOCIATED WITH BREAST IMPLANTS AND CELL PHONES—DRS. JOSEPH FRAUMENI, LOUISE BRINTON, AND PETER INSKIP

Introduction. Dr. Fraumeni noted that epidemiological studies of cancer risk factors tend to attract an unusual amount of attention. Of particular interest, he said, is the role of environmental exposures—such as radiation, occupational exposures, environmental pollution, dietary factors, and consumer products—as cancer risk factors. Studies of these exposures are scientifically challenging when they affect a large segment of the population but the relative risks are low. Moreover, he said, the studies are often subject to great scrutiny when the issue under investigation is of a sensitive or controversial nature, when there are important policy or regulatory implications, or when the outcome of the study has political or economic ramifications. High-visibility studies often become the responsibility of NCI's intramural epidemiology research program because of its ready access to data sources, the speed with which it can launch special studies, and its ability to coordinate multidisciplinary or multicentered studies. Often, external advisory panels made up of a multidisciplinary set of experts and consumer advocates are constituted for high-visibility studies. Members of these panels are selected by the Institute Review Office, which also coordinates these reviews. The panels help ensure that the studies are carried out with the highest level of scientific rigor and insight, and that the studies can withstand the inevitable public scrutiny from special interest groups. Dr. Fraumeni introduced Dr. Louise Brinton, Chief of the Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, to present a high visibility study on the risks of cancer following breast implants.

Breast Implants and Cancer. Dr. Brinton explained that this study was originally begun in the early 1990s. Congress, in its 1992 Senate appropriations bill, encouraged the Institute to develop a strategy for conducting longitudinal studies of silicone breast implants. The rationale for undertaking the study was that a large number of women—estimated to be one to two million to date—have obtained breast implants since they were first marketed. Additionally, there have been anecdotal reports of a variety of possible disease associations with breast implants, but these have been difficult to interpret.

Most of the studies have had limitations such as small sample size, short followup time, or absence of detailed information on such characteristics as type of implant. Lastly, many of the studies have had controversial funding sources. Concerns about possible long-term effects from implants include: breast implant leakage or rupture, which could lead to immunologic or infectious consequences; toxic effects from the silicone or other materials in the implants; the possibility of foreign body response; and interference with mammographic visualization of breast lesions, which could affect the detection of those lesions or the prognosis of breast cancer.

Dr. Brinton's team designed a retrospective cohort study. They identified 13,488 women from 18 plastic surgery practices in southeastern U.S. cities who had had cosmetic bilateral augmentation mammoplasties prior to 1989. In addition, they identified a comparison group of 3,936 women who had had other types of plastic surgery at the same practices. Dr. Brinton and her team were successful in locating about 80 percent of both the implant and the comparison patients. They abstracted medical records for identifiers, implant type, complications, and risk factors; they determined vital status and location information; they obtained detailed questionnaires from over 70 percent of both the implant and comparison groups; and, for patients who had died or who had developed cancer or connective tissue diseases, they attempted to obtain death certificates and medical records to define endpoints more precisely.

Dr. Brinton added that the study presented some logistical challenges. The first challenge was to identify plastic surgeons who would grant the researchers complete access to their medical records. Her team also found that breast implant patients tended to be a mobile group with multiple addresses and name changes, making it difficult to locate them years after their surgeries. The team found it necessary to be sensitive to the concerns of study participants, advocacy groups, and plaintiff lawyers about the unbiased nature of their work. Confidentiality issues were complicated by the fact that many of the implant recipients had never told their families of the nature of their plastic surgery. A final challenge was the high visibility of the study; information on the results has been widely sought, with some requests stemming from litigation. Dr. Brinton said that her team convened a Study Advisory Panel to help with these logistical issues as well as with scientific issues. The panel is comprised of epidemiologists, plastic surgeons, an oncologist, a radiologist, and consumer advocates. She said that the Panel has been very helpful in guiding her team through the complexities of the study.

Findings. The relationship between breast implants and breast cancer risk was the first subject of analysis. The team compared the observed number of breast cancers in both implant patients and comparison patients, with expected numbers based on incidence rates available through the SEER program. The observed numbers were close to the expected numbers. The investigators also computed standardized incidence ratios (SIR), a ratio of observed events to expected events, and found these ratios to be very close to 1.0, indicating no evidence of either an elevation or a reduction in risk. One exception to that finding was evidence of a possible reduction in risk for those patients who had short followup periods. The SIR for patients who were followed for less than 5 years was 0.7, and for those who were followed for 5 to 9 years, the SIR was 0.8. However, after 10 years of followup, there was no evidence of any alteration in risk. Dr. Brinton said that such a finding usually indicates a pre-implantation screening effect—in other words, women who are screened for eligibility for a breast implant and are found to have breast cancer do not enter the cohort. Because breast implants can interfere with the visualization of breast lesions, investigators examined the question of whether breast implant patients are diagnosed at a later stage of the disease. The analysis revealed that the stage of the disease was slightly more advanced

for implant patients than for the comparison group, but this finding was not statistically significant. Moreover, there was very little difference in breast cancer mortality rates. Dr. Brinton said that this finding would be the subject of further study. Dr. Brinton's team is conducting additional analyses, including the risk of cancers other than breast cancer, the risk of mortality from specific causes, and the incidence of connective tissue disorders (especially rheumatoid arthritis, Sjogren's disease, and scleroderma). Dr. Brinton noted that evaluating rheumatological conditions is accompanied by some complexities, which include the intense publicity about possible effects from breast implants leading to reporting biases, the lack of standardized rheumatological criteria, and the suggestion that breast implants may lead to an unrecognized condition comprising a complex of unique symptoms.

Questions and Answers

Dr. Norton asked for more information on the selection of the control group. Dr. Brinton explained that the control group was selected from the same plastic surgery practices that provided the implant patients. The investigators randomly chose patients with conditions that would allow a comparably aged comparison group. One control patient was chosen after about every fourth implant patient. Dr. Norton pointed out that breast cancer patients with implants would have a higher incidence of breast cancer than non-breast cancer patients, and Dr. Brinton replied they had selected patients with cosmetic implants only.

Dr. James French, Director, The Center for Plastic Surgery, asked if Dr. Brinton had analyzed cancer risks based on the type of gel within the implant envelope. Dr. Brinton replied that they had looked at the effects of different types of implants, including silicone gel, saline, double lumen, and polyurethane foam-coated implants.

Dr. Klausner asked Dr. Brinton to comment on the reactions her study has received in terms of validity, acceptability, and credibility. She said that there were many criticisms prior to its being published in *Cancer Causes and Control*, but her team waited to deal with them because they wanted the science to speak for itself. Following publication, she said, there were no complaints about the results.

Dr. Wittes asked Dr. Brinton to comment on how much more difficult starting the study would be today given the increased emphasis on medical confidentiality. Dr. Brinton acknowledged that using the same methodology today would not be possible. The research team probably would have to seek out patients in advance to ask their permission to review their medical records, a process that would hamper response rates and the validity of the study, and would complicate the work of epidemiologists.

Dr. Freedman asked if studies had been done to look at the expansion of T cells at the sites of implants. Dr. Brinton said her understanding was that a number of studies have looked at immunologic repercussions of implants, but so far there is no consensus as to what the consequences might be.

Cellular Telephones and Brain Cancer. Dr. Fraumeni introduced Dr. Peter Inskip, Tenure-Track Investigator, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, to discuss the study findings. Dr. Inskip noted that a possible relationship between cellular phones and brain cancer drew widespread public attention in 1993 because of wide publicity given to lawsuits filed by family members of cellular phone users who developed brain cancer. Congress held hearings on

the issue that year, and NCI decided to add a cellular phone component to a previously planned case-control study on brain cancer. Data collection began in 1994.

The NCI study enrolled 782 newly diagnosed histologically confirmed cases of glioma, meningioma, and acoustic neuroma in hospitals in Phoenix, Boston, and Pittsburgh. His remarks covered only patients with glioma. The team also enrolled about 800 control subjects who had been admitted to the same 3 hospitals for a variety of nonmalignant conditions. Interviews about cell phone use were held with subjects from summer 1994 through summer 1998. Dr. Inskip said the type of cell phone that has elicited concern is the hand-held phone where the antenna is next to the head while the phone is in use. Cell phones operate in the microwave range of the electromagnetic spectrum. Other devices operating in the same range include microwave ovens, radar, and broadcast television. Cellular phones do not represent qualitatively new exposures to radiation—the issue of concern is holding a low-power transmitter next to the head. Microwave radiation operates at a frequency range that is from 1 million to 10 million times lower than that associated with ultraviolet radiation, and still lower than that associated with ionizing radiation such as x-rays. Ionizing radiation can break chemical bonds and damage DNA directly, but microwave radiation can only cause molecular excitations leading to tissue heating, the principle applied by microwave ovens. It does not damage DNA directly. Dr. Inskip noted that concerns about brain cancer have had little effect on the growth of cell phone use. U.S. subscribers to cell phone services numbered about 100,000 in 1984, and that number has grown to about 110 million as of January 2001. If cell phones have adverse health effects, he said, the potential public health implications are considerable.

Findings. Neither those subjects reporting ever having used a cell phone nor those reporting regular (two or more calls per week) use were at increased risk of brain cancer relative to those who had never used a cell phone. Moreover, regular users who used their phones for an hour or more per day showed no increased risk, nor did those who had used cell phones for 5 or more years. The investigators also determined that, among brain cancer patients, there was no tendency for tumors to occur disproportionately more often on the side of the head on which the phone was used. Dr. Inskip reported that three other studies of cell phone use and brain cancer have been published recently, and none of these found any consistent evidence of an increase in risk associated with cell phone use. However, longer-term risks need to be evaluated. Such studies are in progress, Dr. Inskip said, coordinated by the International Agency for Research on Cancer. Dr. Inskip concluded his presentation by reminding Board members that cell phone use was only one component of a study to identify brain cancer risks associated with occupation, medical history, reproductive history, family history, genetic predisposition, diet, and other factors. Their study should produce a rich database on a variety of possible risk factors, he said. Dr. Inskip also thanked the study's Advisory Panel and co-investigators from NCI and collaborating institutions.

Questions and Answers

Dr. Abu-Ghazaleh asked about the frequency of radar waves in radar used by police officers, and if there had been an association made between use of radar and testicular cancer. Dr. Inskip replied that radar uses higher frequencies than the microwaves associated with cell phones, but reports of testicular cancer so far are anecdotal.

Dr. Nienhuis asked Dr. Inskip to estimate the possibility of detecting a significant risk at 10 years of cell phone use that was not apparent at 5 years. Dr. Inskip acknowledged that for some carcinogens,

including ionizing radiation, the excess risk does not appear until after 5 or 10 years. He conceded that it was possible that cell phone use could increase cancer risk over a greater time period. But, he said, ionizing radiation is a demonstrated carcinogen that is known to damage DNA; microwave radiation does not fall into that category. At present there is no reason to assume that cell phone use would pose such a risk.

XVI. FUTURE AGENDA ITEMS—DR. PHILLIP SHARP

Dr. Sharp invited all Board members and members of the public to contact him with any suggestions for future agenda items.

XVII. ADJOURNMENT—DR. PHILLIP SHARP

There being no further business, the open session of the 117th meeting of the National Cancer Advisory Board was adjourned at 11:45 p.m. on Wednesday, February 14, 2001.