DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
January 29-30, 1990

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board

Summary of Meeting*
January 29-30, 1990

The National Cancer Advisory Board (NCAB) reconvened for its 73rd regular meeting at 8:30 a.m., January 29-30, 1990, in Building 31, 6th Floor, Conference Room 10, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown
Dr. John R. Durant
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Howard M. Temin
Dr. Samuel A. Wells

President's Cancer Panel
Dr. Armand Hammer
Dr. William P. Longmire
Dr. John A. Montgomery

***Ex Officio* Members**

Dr. Dorothy Canter, NIEHS
Dr. William Farland, EPA (Absent)
Dr. Roy Fleming, NIOSH
Captain Bimal Ghosh, DOD
Dr. Richard Greene, VA (Absent)
Dr. John R. Johnson, FDA
Dr. Lakshmi Mishra, CPSC
Dr. William F. Raub, NIH
Mr. James S. Robertson, DOE
Dr. Louis W. Sullivan, DHHS (Absent)
Dr. James B. Wyngaarden, OSTP (Absent)
Dr. Ralph E. Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

Dr. Eve Briles, Associate Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science Foundation for Dr. Maryanna Henkart.

Dr. Grace Ann Ehlke, George Mason University, representing the Oncology Nursing Society for Ms. Delores Esparza.

Dr. Robert N. Frelick, Past President, Association of Community Cancer Centers, Wilmington, Delaware, representing the Association of Community Cancer Centers.

Dr. William Garrett, Executive Vice President, National Medical Association, representing the National Medical Association for Dr. Vivian Penn Williams.

Dr. Ed Gelmann, Professor of Medicine and Pharmacology, Georgetown University, Washington, D.C., representing the American Society of Clinical Oncology for Dr. Raymond E. Lenhard, Jr.

Dr. Edwin A. Mirand, Associate Institute Director and Dean of the Roswell Park Memorial Institute Graduate Division, Buffalo, New York, representing the Association of American Cancer Institutes.

Dr. Robert Park, Past President, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists for Dr. Warren Pearse and also the Society of Gynecologic Oncologists for Dr. Clarence Ehrlich, President.

Dr. John F. Potter, Director, Lombardi Cancer Center, Georgetown University, Washington, D.C., representing the American College of Surgeons and the Society of Surgical Oncology.

Ms. Ellen Schillinglaw, Director of Government Relations, American Society of Clinical Oncology.

Dr. John Stevens, Vice President for Research, American Cancer Society, representing the American Cancer Society for Mr. Alan Davis.

In addition to NCI staff members, meeting participants, and guests, a total of 39 registered members of the public attended the meeting.

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF DECEMBER 4-5, 1989, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 73rd meeting of the National Cancer Advisory Board (NCAB) to order and welcomed Board members, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. He invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the December minutes was postponed until the following day's session.

Dr. Korn announced that a memorial service would be held at NIH the following day in memory of Mrs. Rose Kushner, former NCAB member and advocate of the rights of cancer patients. He read the following tribute to Mrs. Kushner, from a memorial scroll prepared on behalf of the Board:

> Rose Kushner was a breast cancer patient, a counselor for patients and their families, an advocate for sensitivity and modernization in breast cancer treatment, and a conscience made visible for the medical community.
>
> She talked, she wrote, she lobbied, she yelled, she argued, and fundamentally, she won. Taboos were broken, and out-of-date ideas fell with a resounding crash. Women need no longer face treatment for breast cancer without evaluating alternatives and considering outcomes. Women have been taught to ask questions and to think for themselves in making crucial decisions.
>
> Generous with her time, on countless occasions Rose Kushner served as an expert witness to the Congress and Federal agencies and as a consultant to professional groups. As a patient advocate, she gave generously to the NCI's Task Force on Breast Cancer. She confronted doctors, and she lobbied insurance companies and legislatures.
>
> She brought to the National Cancer Advisory Board compassion, commitment, and knowledge, and perhaps more than anything else, the courage of her convictions. She gave and she gave. She spoke for breast cancer patients, for women, and ultimately for every human being faced with a terrible disease.
>
> We are glad she was among us. We are the better for it. We remember her today with sadness, and we will remember her for years with admiration.

II. FUTURE MEETING DATES

Dr. Korn called Board members' attention to the following confirmed meeting dates: May 14-16, 1990; October 1-3, 1990; and December 3-5, 1990. To be confirmed are the following dates: February 4-6, 1991; May 6-8, 1991; September 23-25, 1991; and November 25-27, 1991.

Dr. Korn noted that although 3-day meetings continue to be listed, the 2-day format will be used routinely or whenever possible.

III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR. ARMAND HAMMER

Dr. Hammer reported that the Panel held its final meeting in 1989 on the NIH campus. Included on the agenda were presentations by NCI staff as follows: Dr. Charles Myers, Chief of the Medicine Branch, Division of Cancer Treatment (DCT), discussed use of the drug suramin for prostate cancer; Dr. Carmen Allegra, Medicine Branch, DCT, described compounds under

development in the DCT for the treatment of patients with colon and rectal cancer; and Dr. Bruce Chabner, Director of DCT, discussed the training program in regulatory medicine that was developed jointly by NCI and the Food and Drug Administration (FDA). Dr. Hammer noted that the presentations from the NCI staff were impressive and encouraging to the Panel, and he commended the development of the joint training program. He attributed some of the improved cooperation between NCI and FDA to the work of the Lasagna Committee (Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, constituted by the Panel at the request of then-Vice President Bush). Two additional meetings of the Committee are scheduled, one in collaboration with the FDA. The Committee's final report will be submitted by the Panel to President Bush.

Another presentation at the December Panel meeting was Dr. Steven Rosenberg's review of current biological therapies under investigation in the Surgery Branch, DCT, including updates on improved techniques for producing tumor-infiltrating lymphocytes and on gene transfer experiments. The Panel also heard presentations from FDA Commissioner Dr. Frank Young (on improved NCI-FDA cooperation) and from Dr. James O. Mason, Assistant Secretary for Health, Department of Health and Human Services (DHHS). In his presentation, Dr. Mason indicated that one of Secretary Louis Sullivan's major priorities is to enhance and maintain the Nation's biomedical research, the core component of which is the NIH, and he noted the Secretary's great concern about the salaries of scientists. Dr. Hammer stated that the Panel shared this concern.

On behalf of the Panel, Dr. Hammer expressed appreciation for the efforts of Drs. Samuel Broder and Elliott Stonehill and all who participated in the December meeting.

The first Panel meeting of 1990 is scheduled to be held at the Columbia University Comprehensive Cancer Center in New York City. Dr. Hammer said the Panel plans to review recent developments in the field of oncogenes, as well as other significant developments in cancer research and therapy.

Turning next to the proposed NIH conflict-of-interest guidelines for health researchers, Dr. Hammer reported that the Panel was pleased to note that NIH had withdrawn the originally proposed guidelines. He expressed the hope that the new guidelines would to a much greater degree take into consideration the future needs of the scientific community.

Next, Dr. Hammer reported that President Bush had written to acknowledge receipt of the Panel's report and to thank the Panel for a job well done. He added that the President had also expressed appreciation for the effort that was undertaken through *Stop Cancer* to supplement Federal cancer research funds with resources raised through private sources. Dr. Hammer said *Stop Cancer* would provide the NCI with funds this year that would match the $12.5 million designated by the Senate Appropriations Committee and approved by Congress, beginning with a $2.5 million check to be presented that morning. Dr. Hammer noted that this check, when added to the funds previously given to NCI, will bring the total to approximately $3 million, which the NCI will allocate through the normal peer-review process.

In closing, Dr. Hammer commented on the political developments in Eastern Europe in the year just ended, and he expressed the hope for an equally momentous breakthrough in the fight against cancer.

IV. REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE--DR. SAMUEL BRODER

Dr. Broder added his expressions of sympathy about the death of Rose Kushner, and on behalf of NCI expressed sympathy to Dr. Hammer on the loss of his wife. He thanked Dr. Hammer for the Panel's attention to the intramural program and also for the funds received through *Stop Cancer*, noting that they would be used in accord with the normal peer-review procedures. Dr. Broder also recognized the generous contribution to the Gift Fund by

Dr. Gerhard Andlinger to be used to help support and expand basic research and clinical activities related to lymphomas and other lymphatic disorders.

Emphasizing that NCAB members serve until the President appoints their successors, Dr. Broder presented certificates of appreciation to the following members who were completing their terms of service: Mrs. Helene Brown, Dr. Roswell Boutwell, Dr. Gertrude Elion, Dr. David Korn, Dr. Enrico Mihich, and Dr. Louise Strong.

Dr. Broder announced that the Division of Cancer Biology and Diagnosis (DCBD) has been renamed the Division of Cancer Biology, Diagnosis, and Centers (DCBDC). He noted the following staff changes: Dr. Maryann Roper is leaving as Deputy Director; Dr. Emil Freireich, from M.D. Anderson Cancer Center, will assist on special projects in the Office of the Director under an intergovernmental personnel assignment; Dr. Lloyd Law retired as Chief of the Laboratory of Cell Biology, and Dr. Michael Gottesman was appointed to replace him; Dr. James Phang was reassigned as Chief, Laboratory of Nutritional and Molecular Regulation; Dr. Faina Shtern was appointed Chief, Diagnostic Imaging Research Branch; Dr. Flossie Wong-Staal has accepted a position at the University of California at San Diego; and Drs. Allen Schreier and Patricia McCormick have been hired as program directors in the Cancer Centers Branch. Staff awards were as follows: Dr. Barney Lepovetsky and Ms. Dorothy Grant, both in the NCI Office of Technology Development, received NIH Director's awards, and Dr. Donald Henson, DCPC, was elected chairman of the American Joint Committee on Cancer.

Dr. Broder reviewed agenda items noting in particular the report to be presented by Dr. Robert Robinson on the Uptown cigarette issue and the role of the Philadelphia National Black Leadership Initiative on Cancer (NBLIC) in the outcome. He recalled Dr. Louis Sullivan's leadership in originating the NBLIC and described as unprecedented Dr. Sullivan's stand against the introduction of cigarettes targeted to the black community in Philadelphia.

Referring to the constraints on the operating budget, Dr. Broder stated that the Executive Committee had decided to phase out *Cancergrams*, *Oncology Overviews*, and the *Recent Reviews* series covering basic science areas of research. Basic science researchers will have access to the information on NCI's CancerLit data base, which is updated monthly and grows at the rate of over 70,000 new citations annually. NCI will also continue disseminating information through the *Journal of the National Cancer Institute (JNCI)* and other means. The clinical *Cancergrams* and other related information activities will continue. In discussion, Board members expressed support for this decision and suggested a need to ensure that NCI supports the most useful and current modes of communication and information dissemination.

Dr. Broder reported that he had recently met with Soviet Ambassador Dubinin and that as a result, NCI would be exploring new ways of sharing electronic data bases, including PDQ, with the Soviet Union and making available selected publications, such as *JNCI*, on a wide scale to the Soviet Union and Eastern Europe. Other opportunities for scientific and clinical collaboration and information exchange will be explored as well.

Dr. Broder announced that a new set of Cancer Information Service contracts would be awarded shortly. Approximately 17 contracts are expected to be awarded, and with the increased budget for regional offices, they should play an important role in helping comprehensive cancer centers perform their important outreach functions under the new criteria.

Turning to the budget, Dr. Broder announced that the President's FY 1991 budget could not be discussed until after its official submission to the Congress later that day. The appropriated FY 1990 budget of $1.664 billion has been subjected to a 1.3 percent sequestration or $23 million, and additional reductions of approximately $10 million for procurement reform, the extramural salary cap, construction redirection, and the DHHS salary reduction. It was noted that NCI has a strong program of peer-reviewed construction grants and may receive some of the pooled NIH construction funds. In addition a new agency, the Agency for Health Care Policy and Research,

has been established, and funds may be tapped from other Public Health Service (PHS) agencies for its support. The NCI share of an overall NIH assessment would be about $6 million.

Dr. Broder pointed out that the FY 1990 operating budget represented about a 3.8 percent or $60 million increase over the FY 1989 actual budget. The cancer budget received an increase of about 2.2 percent, and the AIDS budget about 23 percent. Dr. Broder said that $748 million for research project grants will enable funding of approved grants at about 90 percent of recommended levels. Because of the normal cycling and mix of grants, almost all of the $26 million increase to the research projects grant pool will be for competing grants. The total number of competing grants is expected to remain at the same approximate level as in 1989. The percent funded is projected at about 26 percent, with downward negotiations of about 10 percent for competing grants and about 4 percent for noncompeting grants.

In discussion, it was suggested that it might be useful to have a future presentation on NCI's information systems, the resources committed to these activities, future plans, and statutory obligations. Ms. Susan Hubbard noted that a user survey had been conducted, and although respondents found the *Cancergrams* useful, there was a need to establish priorities among the various information products.

V. ROLE OF THE NBLIC IN A COMMUNITY STRUGGLE AGAINST THE TOBACCO INDUSTRY: THE PHILADELPHIA EXPERIENCE--DR. ROBERT ROBINSON

Dr. Robinson began by calling attention to the distinction made by Dr. Sullivan between the right of corporations to pursue profit and the need to evaluate corporate behavior within a context of social responsibility. Similarly, he noted that Dr. Broder's emphasis on African American, Hispanic, and poor populations properly puts science within a moral context.

As background, Dr. Robinson stated that Philadelphia had led the country in the development of impacted ghettos, which are characterized by high unemployment and single heads of households and correlate strongly with the flight of employment and corporations from the inner city to the suburbs. He described Philadelphia as very underdeveloped in terms of its inner-city infrastructure. He stated further that, when mortality data are adjusted for age and gender, cancer is the leading cause of death for African Americans in Philadelphia.

Dr. Robinson recalled that representatives from Philadelphia, led by Dr. Maurice Clifford, Commissioner of Health, had attended the regional NBLIC meeting held in Washington, D.C., which was chaired by Dr. Reed Tuckson. The Philadelphia group took to heart Dr. Tuckson's message to return to their community to organize locally, reach out, and do something about the devastating problem of cancer incidence and mortality among African Americans. Dr. Robinson said that the first principle of the Philadelphia organization is that it is very inclusive, involving representatives from the American Cancer Society, church groups, the Medical Society of Eastern Pennsylvania, the National Health Care Professionals organization, the Committee to Prevent Cancer Among Blacks, and the American Lung Association, among others. Therefore, a coalition of leaders was already in place and the Coalition Against Uptown Cigarettes was a logical consequence of the NBLIC commitment to doing the right thing for the African American community in Philadelphia.

Dr. Robinson pointed out that the Coalition Against Uptown Cigarettes was not an anti-smoking movement; nor was it set against media advertisers of cigarettes. Indeed, the group felt that to take such a position would imperil the economic security of institutions that are embedded in the African American community, and would divide the community struggle against Uptown cigarettes. Because the Coalition sought to avoid any course that would be divisive to the African American community, that issue was not raised.

Next Dr. Robinson discussed the issues that were germane to the campaign against Uptown cigarettes, the obvious one being that the product was to be introduced into a vulnerable

community that was already suffering disproportionate incidence of and mortality from cancer and heart disease. He noted that because the vulnerability of the community is based on educational and economic status, the tobacco industry contends that to defend that community against the right to buy a product is paternalistic. Dr. Robinson said that figuring out how to talk about a population's vulnerability without being paternalistic is a complex challenge.

Dr. Robinson identified the second issue as that of choice: the tobacco industry asserts that people have a right to make a choice, but their practice of blanketing a community with billboard advertising does not allow any choice. There are many more billboards in African American communities than elsewhere, and more than half of those billboards advertise cigarettes.

Another issue is the high nicotine and menthol characteristics of Uptown cigarettes. Dr. Robinson stated that the only other cigarettes made by R.J. Reynolds with higher nicotine and tar levels are unfiltered Camels. This issue is also related to the issue of choice because by bringing a strongly addictive product into a community, choice is eliminated. In addition, Dr. Robinson pointed out that over 60 percent of African Americans smoke menthol cigarettes, but those most likely to do so are between the ages of 15 and 25. He suggested that what R.J. Reynolds was doing was creating a new generation of addicted smokers. The Coalition was determined to defend the future of the African American community and preserve self-determination and community control. As a related issue, Dr. Robinson noted that cigarettes exported to Third World countries have higher tar and nicotine levels than cigarettes sold in the United States.

Finally, Dr. Robinson emphasized the critical issues of social responsibility and ethics, which also were strongly reinforced by Dr. Sullivan. It was known ahead of time that Uptown cigarettes would cause higher levels of disease and death; so an aware community could not allow the introduction of such a product.

In terms of implications for the future, Dr. Robinson suggested a need to confront the authoritarianism of the tobacco industry and its assumptions that because it has a legal product, it has the right to do anything with that product, regardless of the consequences. The antismoking struggle for the 1990s needs to focus on African American and Hispanic populations.

The following points were raised in discussion:

- A useful antismoking approach for African American communities as well as for teenagers might focus on lifestyle rather than health issues.
- The Coalition's efforts would have escalated if R.J. Reynolds had not capitulated.
- Successful efforts to combat tobacco and alcohol billboard advertising have involved getting other corporations to sponsor the space.
- Although many groups were involved, the leadership of the Coalition was clearly African American.
- The Philadelphia effort involved both outreach to the media and community organizing.
- NCI has issued an RFA for cancer control activities in Hispanic populations.

VI. ACCEPTANCE OF LARGE PRINCIPAL INVESTIGATOR-INITIATED GRANTS: A DISCUSSION--MRS. BARBARA BYNUM

As background for the discussion on NCI acceptance of large principal investigator-initiated grants, Mrs. Bynum referred Board members to research project grant (RPG) information contained in documents previously distributed, including copies of three R01 grant applications

received recently in the referral office of NCI as examples of the type of application under discussion. She noted that NCI's acceptance of these assignments indicates that all three of the large investigator-initiated grants have high relevance to the cancer program. She then summarized the grant trends and ranges of awards for R01s and P01s over the past 3 years and pointed out that the average direct cost of new and competing R01s awarded by NCI in 1989 was $122,000; P01s awarded in that same period averaged $685,000. R01s exceeding $500,000 have never represented more than 1 percent of the total of R01 dollars awarded. Mrs. Bynum noted that one of the three applications under discussion had a first year direct cost request of $3.09 million (for acquisition of hardware), which would be roughly equivalent to the award of 25 "average-sized" R01s or 4 "average-sized" P01s in 1989. Finally, Mrs. Bynum reminded the Board that other Institutes have established large grant policies and a recently published NIH guide announcement indicates that applicant investigators should inform themselves of such policies prior to preparation and submission of large grant requests. This announcement included the statement that different Institutes have different dollar limits for applications and those that exceed the limits will be returned without review.

Mrs. Bynum recalled that in December, Dr. Broder had requested Board advice as to whether NCI should continue its current practice of accepting and reviewing grant applications without regard to the requested level of funding. She identified three issues to be considered: (1) Should NCI establish a dollar limit for unsolicited RPGs in general or in some specific category, or should some other restriction be placed on the acceptance of large grants? (2) If a dollar limit is contemplated, what should the amount be? (3) Should NCI retain its present policy, which includes informing NCAB members before the meeting of the receipt of grants in excess of a predetermined amount (currently $1 million) and dealing with such applications on a case-by-case basis, with emphasis primarily on the science of the grant proposal.

In discussion, the following points were made:

- Large grants do raise special policy considerations; therefore it is important that the Board continue reviewing them in their entirety before the meeting.

- Based on recent debates at NCAB meetings, a useful first step might be for NCI to develop an adaptation of the proposed National Heart, Lung, and Blood Institute (NHLBI) policy that calls for concept review by staff prior to peer review to consider the desirability of alternative mechanisms for large projects.

- In practice, large R01s because of their complexity have usually been evaluated according to the procedure used for P01s (by a special peer-review committee); some NCAB members feel they should be reviewed by a chartered study section to ensure a more comparative evaluation.

- NCI's present policy provides flexibility and ensures that independently initiated projects with scientific merit, whatever the cost, can be considered for funding.

- NCAB review problems tend to be associated with applications reviewed by special study sections because those grants cannot be percentiled; in this sense, they cannot be considered or evaluated in the context of the whole portfolio of grants and in relation to available resources.

- By their nature, some projects (e.g., clinical trials) do not have definitive long-term end points within the project period that might allow for interim review or for decisions to be made on continuing at the end of the award period. Such projects may require qualitatively as well as quantitatively different decisions as to their priority in terms of funding commitments from the R01-P01 grant pool, compared to that of traditional grants. A policy like that proposed by NHLBI would provide an opportunity for early intervention, if necessary.

Dr. Broder emphasized that the R01 mechanism is designed to support investigator-initiated research and is a cornerstone of the research effort. However, large multiyear grant applications pose a real problem both in the initial impact against the R01 pool and in the out-year commitment cost, which can reduce the funds available for other applications for many years. He emphasized the need for advice from the Board as to the best way to handle the problem.

Dr. Korn moved that the NHLBI model be adapted to meet the needs of NCI and brought back to the May meeting as a policy recommendation to the Board. The motion was seconded and approved unanimously.

Items suggested that require consideration in developing the proposed policy included provisions for identifying appropriate alternative instruments and seeking creative solutions to the problem of expensive equipment needed for some programs (e.g., radiation research) so that grants in those areas are not automatically excluded.

VII. REMARKS BY THE ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH--DR. WILLIAM RAUB

Dr. Raub stated that more than 700 comments had been received on the draft conflict-of-interest guidelines published last fall. These comments are now being analyzed, and Dr. Sullivan has indicated that the normal rulemaking process will be followed, if any regulations are judged to be necessary. This regulatory process ensures not only consideration of the subject of the rules but also their impact on economic conditions.

Dr. Raub said that NIH's involvement in the issue was based on several assumptions: (1) the efficient transfer of research results into commerce is essential if the United States is to maintain and enhance its economic competitiveness; (2) the biotechnology industry illustrates the special importance of successful technology transfer from publicly financed activities to the private sector; (3) the national statutes enacted during the 1980s embodied strong public expectations that tax-financed research institutions would give high priority to ensuring commercialization of their scientific results, wherever appropriate; (4) cautious attitudes prevail about interactions between the public and private sectors; (5) the rapidly evolving relationships among government, academia, and industry with respect to technology transfer have outgrown the rules and mores that once were sufficient protection against individual and organizational conflicts of interest; (6) the research community will not maintain public confidence without new rules that harmonize national, industrial, and individual interests; and (7) special attention must be given to the tax-financed evaluations of commercial products and the commercialization of tax-financed inventions.

Defining the commercial product as one that is either manufactured for sale or is undergoing premarket development and evaluation, Dr. Raub said that the dilemma recently encountered is that when a privately owned commercial product was discovered or developed through publicly financed research and development, conflicts of interest can arise, at least in appearance if not in fact. The prospect of monetary reward resulting from successful commercialization can and has led to biased interpretation of data, selective reporting of research results and nondisclosure of others, and falsification and fabrication of records or reports.

Dr. Raub suggested several approaches in responding to comments to the draft guidelines. It might be useful to identify some broadly acceptable minimum level for personal financial interest, unless any financial holding is considered to constitute a conflict. Perhaps attention need only be focused on development and evaluation activities, such as Phase III and IV clinical trials. Another approach might consider whether full public disclosure of an individual's financial interest would be an acceptable alternative to divestiture. It will also be necessary to define under what circumstances, if any, an investigator can be a paid consultant to a manufacturer during the course of an NIH-funded project.

Dr. Raub noted a similar set of concerns associated with the commercialization of tax-financed inventions. The patent and trademark amendments of 1980 were designed to encourage not-for-profit institutions and small businesses to commercialize inventions made by their scientists under grants or contracts awarded by the Federal Government. The awardee institutions are automatically awarded first rights to such inventions and the Federal Government retains secondary rights, such as the option to obtain a royalty-free option. The Technology Transfer Act of 1986 created similar rights and obligations for laboratories operated by the Federal Government. Dr. Raub pointed out that during the 1980s, various institutional arrangements proved to be efficacious in facilitating technology transfer from noncommercial organizations to their commercial partners. These can be multiproject pacts, e.g., the Washington University-Monsanto Agreement, or single project arrangements like the NIH collaborative research and development awards (CRADAs). These arrangements provide for the sharing of ideas and resources, sharing of data before publication or patent filing, and development of nonexclusive licensing arrangements, whereby the noncommercial partner gains a revenue stream if the product becomes a commercial success. Problems can and do arise when the investigator who made the tax-financed invention treats it as his or her personal intellectual property rather than the property of the awardee institution.

Dr. Raub stated that these and other issues will need to be addressed in developing new rules to help awardee institutions and scientists commercialize inventions appropriately. However, the first step in the regulatory process, the publication of a notice of proposed rulemaking, still appears premature. NIH will soon present a set of options for next steps to the Assistant Secretary for Health Mason, and Secretary Sullivan. In particular, Dr. Raub said that NIH has been asked to look at approaches such as another major conference at NIH, perhaps coupled with a series of smaller regional meetings. He offered assurances that whatever approach is selected, NIH will seek to ensure broad participation by representatives of both the research community and the financial community, as well as other interested parties. Dr. Raub concluded by emphasizing NIH's commitment to fostering technology transfer to the greatest extent that is consistent with the prudent stewardship of public money.

In discussion, Dr. Raub said that in drafting the guidelines, some assumptions had been made that were probably not warranted. For example, it was assumed that most research-intensive institutions know how to effect technology transfer without getting into conflict-of-interest situations; whereas, comments on the guidelines appear to indicate that is not always the case. There is some misunderstanding of the 1980 amendments to the Technology Transfer Act, which specify that the rights reside with the institution not the individual. Dr. Broder stated that his personal perspective was in support of full disclosure and full dissemination of knowledge to the general domain. He said he was concerned that employee inventors would be found in conflict of interest simply by participating in required arrangements between their institutions and the Government. The National Drug Discovery Groups, for example, are expressly for the purpose of fostering interactions among academia, private industry, and NIH. Dr. Broder expressed his view that the academic sector is basically very honest, and those few who are not should be dealt with on an individual basis, rather than imposing stringent regulations on everyone.

Dr. Raub agreed that disclosure would have to be a centerpiece of any action relating to conflict of interest, but he raised the question of what happens when disclosure reveals a genuine conflict of interest and thereby devalues something that has been paid for with public funds. Dr. Chabner emphasized that the timely transfer of ideas is essential for maintaining our technological advantage.

Other points raised in discussion included the following:

- NIH holds an annual technology fair to enable intramural scientists to present their potentially marketable ideas or products to representatives from industry, and perhaps identify outside collaborators.

- Scientific collaborations are essential, as are requirements for disclosure and punishments if disclosure is not made.

- Special consideration may have to be given to equity issues.

In response to Dr. Korn's request that he address the issue of the $15 million (less $200 K for sequestration) NIH fund for facilities, Dr. Raub said that the issue is now under consideration in the Office of the Secretary, with questions from the White House, Congress, and some specific recommendations from NIH. He noted that much of the impetus for the funding is associated with the fire at Jackson Laboratories, and a request for applications (RFA) will be issued for a mouse facility. Another RFA will relate to other types of construction, i.e., for cancer centers and other projects as identified in a Senate report. Dr. Raub said that the amount for the mouse facility will be determined through the peer review of construction grants but will constitute a substantial portion of the $14.8 million.

VIII. LEGISLATIVE UPDATE--MS. DOROTHY TISEVICH

Ms. Tisevich referred Board members to the package that was distributed highlighting legislative activity of interest. In discussing reauthorization issues, she noted that NCI was reauthorized in 1988 for a 2-year period and would be going through the process again this year.

Items of particular interest included the repeal of the Medicare Catastrophic Coverage Act, which eliminated a provision for covering mammography screening. Ms. Tisevich pointed out that several bills have been introduced that will provide coverage for mammography through amendments to the Social Security Act. Provisions of the Omnibus Budget Reconciliation Act include coverage for (1) screening pap smears every 3 years, and more frequently for women at high risk, (2) implementing the sequestration of 1990 appropriations, and (3) establishing a new agency, the Agency for Health Care Policy and Research, in the PHS. Funding for the new agency is to be provided through appropriations, a tap on PHS agencies, and Medicare trust funds. Other significant bills pending before Congress relate to animal welfare issues, including five break-in bills; establishment of a center for tobacco products within the Centers for Disease Control (CDC); establishment of a nonprofit foundation for biomedical research as an agency of the Federal Government to support intramural research at NIH and ADAMHA; other biomedical research issues, including facilities construction and salaries for senior level researchers; tobacco; and AIDS.

Ms. Tisevich also called attention to a provision in the Department of the Interior appropriations bill that expands an existing prohibition on the use of Federal funds for lobbying activities, effective December 23, 1989. Recipients of Federal grants, cooperative agreements, contracts, or loans must certify that Federal funds will not be used for such activities. The provision is being implemented as awards are made.

Finally, Ms. Tisevich noted that the Department of the Treasury appropriations bill includes a provision to permanently ban smoking on all U.S. commercial airline flights of 6 hours or less, effective February 25, 1990.

IX. REVIEW OF NIH BIOMEDICAL TRAINING PROGRAMS, CLINICAL ASPECTS OF TRAINING REPORT--DRS. ALAN RABSON, BRUCE CHABNER, AND VINCENT CAIROLI

NIH BIOMEDICAL TRAINING PROGRAMS--DR. RABSON

Dr. Rabson reviewed the final report on NIH biomedical training programs and requested the Board's advice and consideration of the recommendations. He reported that the review of NIH biomedical research training programs was instituted in April 1989 by Dr. James

Wyngaarden, then Director of NIH, who set up three task forces and a steering committee under Dr. Claude L'Enfant, Director of the National Heart, Lung, and Blood Institute.

Dr. Rabson listed each task force's area of investigation as follows: physician-scientist training, chaired by Dr. L'Enfant; training opportunities in clinical community-based study designs and methodology, chaired by Dr. Carl Kupfer, Director of the National Eye Institute; and predoctoral and postdoctoral training of nonphysician scientists, chaired by Dr. Ruth Kirchstein, Director of the National Institute of General Medical Sciences.

Representatives from each Institute were given the opportunity to take part in the task forces. From NCI, Dr. Chabner participated in the physician-scientist training task force, Dr. Greenwald in the community-based study designs task force, and Dr. Rabson in the nonphysician-training task force. Each task force was charged with reviewing NIH biomedical research programs, identifying and assessing issues, and making recommendations.

PHYSICIAN-SCIENTIST TRAINING--DR. CHABNER

Dr. Chabner began by listing the major problems addressed by the committee:

- NIH is not training enough physician scientists.
- More than 60 percent of MDs who participate in research training do so for 12 months or less and then go into practice rather than research careers.
- T32 research-training grant positions often support clinical training instead of producing competitive physicians in the research field.
- Some research training grants have been ineffective in producing physician scientists.

Dr. Chabner went on to enumerate the following issues addressed by the task force: (1) recruitment of talented individuals into biomedical research careers at an early stage, i.e., provide physicians in medical school with an early research experience; (2) optimization of the structure of the postdoctoral research training period for supporting research; (3) integration of research training with clinical certification requirements; (4) identification of new approaches and opportunities for research training; and (5) development of a system to collect data and monitor and evaluate whether the fellowships mechanisms do promote research careers.

With regard to early recruitment, Dr. Chabner said the task force recommended that professional predoctoral students, primarily physicians, be eligible for training on institutional research training grants during elective periods of 3 to 12 months. To optimize structure, it was recommended that research training candidates should invest a minimum of 2 years in light of the positive correlation between duration of research training and subsequent successful pursuit of a research career. To increase trainee commitment, research training experience on an institutional training grant should be extended to 2 years and the pay-back system modified. Following the 2-year experience, the trainee would be expected to continue career development for up to 3 years. A rigorous review of the training programs would be an essential component of the revised structure.

Dr. Chabner went on to summarize the revised research training concept, which would cover a 5-year span. He noted that the major changes were to take place in the first 2 years, which would be on an institutional training grant (T32). The next 3 years would be on either an individual training grant (F32) or a 3-year K-series award. Candidates needing additional training could continue on the T32 for up to 4 years; candidates who have their own project could enter a competive phase by applying for a F32; and candidates wanting their own award could apply for an individual or K-series awards.

Dr. Chabner noted that changing the structure would not solve all the problems, e.g., salaries paid in the T32 program, as well as funding guarantees for undertaking research careers, are inadequate and may discourage even those candidates interested in research careers. He suggested that raising research training salaries and investing in stipends and guarantees for research support following initial training would help solve this problem.

During the discussion, the following points and questions were raised:

- The main concern should not be recruiting candidates for the research training program but increasing funding possibilities for candidates who complete training.
- Internal medicine subspecialties are not attracting the number and quality of people into research that they were 10 to 15 years ago.
- It is essential to have a training grant mechanism to interest people in the laboratory during their residency.
- In the field of surgery, if not in other medical fields, preparation for specialty tracks does not necessitate as much training as is currently required. A certain part of the training period could be replaced by at least 2 years of research or more, if the candidate wants to become competitive in terms of obtaining grants.
- Institutions should make a supportive commitment to their best candidates, at some point in the training program, to ensure candidates the opportunity of using what they have learned.
- Consideration should be given to whether MD students should be required to do a research training program in addition to a clinical specialty training program.
- The whole structure of training programs may be obsolete, given the realities of research and the funding of research in this country today.

TRAINING OPPORTUNITIES--DR. CAIROLI

Dr. Cairoli reported on the second task force's efforts to address the issue of high-priority areas with inadequate levels of training. Greater research opportunities opening up in the areas of treatment, prevention, and behavior are eliciting a corresponding need for training in population-based type studies, i.e., in the areas of biostatistics, clinical trials, and epidemiology. Dr. Cairoli noted that supporting advanced study programs and K-series awards in these three areas would increase pre- and postdoctoral research training opportunities. He remarked that task force recommendations included using current NIH mechanisms more creatively, and implementing the individual predoctoral fellowships under National Research Service Awards in such a way as to increase the number of institutions available for training. Adequate collection of data and evaluation were also emphasized.

NONPHYSICIAN-SCIENTIST TRAINING -- DR. CAIROLI

Dr. Cairoli then went on to discuss the third task force on nonphysician-scientist training, noting that this group was satisfied with the training of nonphysician scientists. Issues of concern were the cost of education and adequacy of stipends. The task force concluded that a two-tier cost of education allowance for predoctoral training, i.e., one level for private institutions and another for public institutions, would control the portion of the NIH training budget allocated to educational expenses. The mechanisms for research training support should be made comparable across Federal agencies, and stipends would increase only when Congress allocated additional monies.

Dr. Cairoli reported on the critical issue of data collection, monitoring, and evaluation, noting that the problem of not being able to compare data from NIH's different data bases, i.e., the consolidated grant data base, the trainee data base, and the payback data base, will be solved when several subcommittees decide on what uniform data all institutions should collect in addition to their own specialized data.

With respect to T32s, Dr. Cairoli stated that they are reviewed by each Institute rather than the Division of Research Grants. The review is based on scientific merit, i.e., adequacy of resources for training, the training record, and where trainees go following training. The second level of review involves three Board members who were assigned responsibility for that specific program area.

Dr. Temin suggested that the entire Board should consider the training grants to determine what fields are most needy and that the review of these grants should have a programmatic as well as a scientific aspect. Dr. Korn pointed out that for nonpublic institutions, tuition falls short of covering the real costs of education. When costs are not met through a training program, they are shifted to another source of revenue.

X. REPORT OF THE SUBCOMMITTEE ON CANCER CENTERS--DR. JOHN DURANT

Dr. Durant reported that the Subcommittee on Cancer Centers met to review the 47-page first draft of NCI's Five-Year Plan for Cancer Centers. He recalled that the plan was developed in response to a recommendation in the Institute of Medicine study that was undertaken at the request of Congress. It was decided that the subcommittee will hold a 1-day meeting at a central location after all comments on the draft have been received to consider the comments from center directors, elected ad hoc advisors, and others and to provide guidance to NCI staff. Dr. Broder added that comments are invited and welcome from all components of the scientific community and from the public at large. Dr. Durant noted that the working meeting would be an open meeting to ensure that a broad consensus of opinion is represented in the final product, which will be submitted to the Board for discussion and approval.

XI. REPORT OF THE WORKING GROUP OF THE SUBCOMMITTEE ON AGENDA--DR. LOUISE STRONG

Dr. Strong reported that the Working Group of the Subcommittee on Agenda met to evaluate its original recommendations for changes and their implementation in subsequent meetings, particularly the annual program review. The following additional recommendations were presented by Dr. Strong on behalf of the Working Group:

(1) Equal time should be allotted for presentations and discussion. Policy discussions should be highlighted and allowed more time.

(2) Written materials relevant to agenda items should be sent to Board members well in advance of meetings.

(3) Administrative information included in written materials should not be repeated in slides.

(4) The 2-day format is endorsed with the recommendation that both days begin at 8:00 a.m. and that subcommittee meetings not be scheduled for Sunday evening. Subcommittee meetings that need to consider major long-term issues should be scheduled for times apart from the 2 days of the NCAB meeting. In addition, subcommittees should consider meeting at 7:00 a.m. or 12:00 noon on Monday or Tuesday.

(5) Overall information (e.g., summaries of trends, allocations by mechanism) should be provided as a regular agenda item each year at the January NCAB meeting.

The report of the Working Group of the Subcommittee on Agenda was unanimously approved.

XII. DIET AND CANCER: A DISCUSSION OF PUBLIC GUIDANCE--DRS. PETER GREENWALD, J. MICHAEL McGINNIS, LUISE LIGHT, AND C. WAYNE CALLAWAY

Dr. Greenwald introduced the discussion of diet and cancer suggested by Dr. Boutwell at the December 1989 Board meeting by citing two recent reviews of research on diet and cancer: *The Surgeon General's Report on Nutrition and Health* and the National Academy of Science's (NAS) Food and Nutrition Board's *Diet and Health Report*. He explained that an ad hoc committee review of NCI's dietary guidance for cancer prevention is underway.

Dr. McGinnis (Director, Office of Disease Prevention, and Deputy Assistant Secretary for Health, PHS), who chaired the DHHS Nutrition Policy Board's effort in developing *The Surgeon General's Report on Nutrition and Health*, explained that because of the number and variety of the cases of death in which diet plays a part, in 1984 it was decided to coordinate the Report from a DHHS central office to include the efforts of the many DHHS agencies involved in nutrition research. He stated that the Report was issued in 1988 and that its 4-year preparation involved more than 50 authors and 200 reviewers, with NIH agencies assuming a substantial share of the responsibility for the preparation of the Report. He noted that the Report is comprehensive in focus, reviewing most prominently the issues related to control of chronic disease, including coronary heart disease, high blood pressure, cancer, diabetes, and obesity, but also addressing issues related to normal growth and development and to drug-nutrient interactions and dietary fads and frauds.

Dr. McGinnis indicated that the major conclusions of the Report relate to the (1) strength of the contribution of diet to health prospects, (2) convergence of recommendations from the perspective of several chronic diseases, and (3) role of dietary fat as a primary factor in the relationship between diet and health. The Report states that for the two out of three adult Americans who do not smoke or drink excessively, diet seems to influence long-term health more than any other personal choice. The evidence presented in the Report suggests that similar dietary patterns affect the risk for several chronic diseases, and similar recommendations for reducing fats, controlling calories, increasing starch and fiber, reducing sodium, and controlling alcohol intake are given for these diseases. The third major conclusion of the Report is the recommendation to reduce total intake of fats, especially saturated fats, because of their relationship to the development of several chronic diseases. The Report provides recommendations for the general population and for specific segments of the population and also provides a series of public policy recommendations.

Dr. Light (Diet and Cancer Branch, DCPC), who has been responsible for the ongoing ad hoc committee review of the NCI dietary guidelines, began her presentation by explaining the procedures for updating the guidelines. She stated that this series of procedures includes internal staff review followed by external ad hoc working group review and then staff review and presentation of the ad hoc working group findings to the DCPC Board of Scientific Counselors (BSC). She noted that the recommendations resulting from the current review of the guidelines will probably be presented at the May 1990 DCPC BSC meeting. She listed the main conclusions of the ad hoc working group, as follows:

- Scientific basis for guidelines is now stronger.
- Individual guidelines should lead with the positive.
- Consistency with other guidelines should be increased.
- The variety of protective factors in vegetables, fruits, and grains should be stressed.

- The obesity guideline should be changed to reflect newer concepts.
- Risk from salt-cured and pickled foods is small in the United States.
- There is no basis for guidelines for high-risk groups.
- Recommendations apply to adults and children older than 2 years.

Dr. Light also reviewed specific word changes in the guidelines suggested by the working group, including specific serving recommendations for whole grain breads and cereals and for fruits and vegetables, a guideline to balance caloric intake and physical activity to maintain appropriate body weight for the general public, and a modification to clarify that the NCI is not recommending drinking alcohol.

In response to a question from Dr. Temin about any known effects on the U.S. diet of the recommendations that were published in the 1980s, Dr. Light outlined a series of changes in the U.S. diet since the 1960s in terms of consumption of more low-fat products, less meat, and more vegetables, as well as some indication in the last few years of an increase in consumption of high-fiber foods. Dr. Greenwald noted that women with higher education tend to have the most healthful diets, and that diet and differential cancer rates continue to pose greater problems in minority and lower income groups. He referred to limited NCI-funded projects for implementation of dietary guidelines, including one project by NAS and an effort in the Office of Cancer Communications with a strong component on cancer prevention awareness.

Dr. Callaway, who was acting director of the NAS Food and Nutrition Board during the development of *The Diet and Health Report*, explained his view of the interaction of science, dietary advice, and public policy as involving four separate categories of activity: data collection and analysis; expert analysis, including review of sufficient data from several species by a group of experts who represent legitimate divergence of opinion; development of public health policy recommendations, ensuring that recommendations made to reduce the risk of one disease do not increase the risk of developing another; and implementation of public policy. He stressed the importance of NCI issuing general dietary guidelines that promote a healthy diet and life style, and being cautious about stating specifically that reducing or increasing a particular dietary component will affect the incidence of specific cancers. He expressed the opinion that it often is inappropriate to make recommendations that are specific to a single disease and that competing risks and the morbidity and mortality patterns of the community must be considered.

In discussion, Dr. Callaway emphasized that resources outside the NCI, such as the NAS and Surgeon General's Reports and ad hoc expert review groups, should be used to broaden the base of consensus for guidelines.

In response to a question from Mrs. Brown about whether there was evidence that the population had followed previous dietary guidelines recommending servings from the four basic food groups, Dr. Light commented that a very small percentage of the population had conformed to the recommendations after 25 years, attributing this to the fact that those recommendations were very general and hard to follow. She urged that the dietary guidelines be specific, simple, and concrete. Dr. Greenwald concurred and added that serving healthful meals in school lunches would serve an exemplary role. He cited the problem of overpromotion of any single published study, such as the recent article disputing the value of eating oat bran in relation to cholesterol, and he re-emphasized the importance of consensus review of data on diet and health to develop guidelines. Dr McGinnis stressed the need for NIH to actively promote consistent dietary quidelines to balance the information the public receives about nutrition and foods from other sources. Dr. Callaway added that it is inappropriate for an organization or institution to endorse specific foods as healthy because the real concern is overall diet.

Dr. Temin initiated a discussion about the necessity for large-scale grants for clinical trials of diets. Dr. Callaway commented that there are considerable data from epidemiologic, intervention, and animal studies that support an association between diet and several diseases and noted that clinical trials are extremely expensive. Nevertheless, he expressed the opinion that a clinical trial of low-fat diet and breast cancer should be conducted.

Dr. Boutwell presented data from animal studies illustrating that caloric intake is a key mechanism through which dietary fat affects the incidence of mammary cancer. He added that because the glycolysis cycle for the breakdown of fat, protein, and carbohydrates is conserved from lower species through mammals, the data from animal studies are transferable to humans, thus negating the need for the NCI to fund future clinical trials of diet and breast cancer. Dr. Boutwell also expressed agreement with the plan to emphasize the positive effect on health of consuming fruits, vegetables, and whole grains, noting also that many components of natural foods inhibit cancer in experimental animals and some are likely to have the same effect in humans.

XIII. CLOSED SESSION

A portion of the second day of meetings was closed to the public because it was devoted to the Board's review of grant applications. A total of 1,257 applications were received, requesting support in the amount of $232,141,742. Of these, 1,192 were recommended for funding at a total cost of $190,135,942.

XIV. CANCER THERAPY EVALUATION PROGRAM--DR. MICHAEL FRIEDMAN

Dr. Friedman announced that he would review some of the past year's activities of the Cancer Therapy Evaluation Program (CTEP) and outline plans for future activities. He invited the comments and suggestions from Board members on the plans that he would present, and he welcomed inquiries on areas of particular concern. He began by pointing out the variety of different funding mechanisms that are employed by CTEP in administering a large investigator-initiated grant and cooperative group program engaged in clinical trials and other projects devoted to the development of new agents, including cytotoxins, biologics, and monoclonals. He listed the four branches of CTEP (Biometrics Research, Clinical Investigations, Investigational Drug, and Regulatory Affairs) and briefly described their functions.

LEVAMISOLE AND 5-FU: CLINICAL ALERTS AND UPDATES

To illustrate the work of the CTEP over the past year, Dr. Friedman related the events surrounding the levamisole-5-FU trials. He reviewed the clinical data from the series of clinical trials in patients with completely resected large bowel cancer. He noted that (1) there is a clearly described pathologic system of prognostic significance based upon clinical findings made at surgery; (2) there is a large group of patients, especially Dukes' B2 and C, where surgery is not curative, although all visible tumor is removed; and (3) there is an opportunity for effective systemic therapies in these patients. Until recently, clinicians did not think such therapy existed.

Dr. Friedman said the drug of interest was levamisole, which has a clearly defined antihelminthic, antiparasitic activity and a poorly defined antitumor effect. Clinical trials with levamisole were initiated in May 1978 by the North Central Cancer Treatment Group (NCCTG). Four-hundred patients with colon cancer were completely resected and then randomly allocated to one of three groups. The results indicated a benefit for recurrences at 5 years and time to recurrence in favor of the levamisole and 5-FU group. One of the subset analyses suggested that for Dukes' C patients, there was an overall survival benefit. Dr. Friedman noted that an intergroup trial was initiated in January 1985, with assistance from the Biometrics and Clinical Investigations Branches of CTEP, to corroborate the findings of the NCCTG trial. Dr. Friedman stated that the results of the second trial were exactly the same and that, statistically, the benefit

was unlikely to be due to chance alone. Group C designation for levamisole was granted by the FDA to the corporate sponsor, Janssen Pharmaceuticals, in May 1989.

To make this information on levamisole and 5-FU therapy available to physicians, patients, and the general public, CTEP issued a clinical update (October 1989) in conjunction with the *Journal of Clinical Oncology* publication of the NCCTG study. Dr. Friedman said that the FDA was scheduled to meet within the week to consider Janssen's new drug application (NDA) for levamisole, and that publication of the intergroup findings was expected in February 1990. He conveyed his appreciation to the FDA for the prompt handling of the levamisole group C request and to Janssen Pharmaceuticals for their cooperation.

Recalling the concern raised by the clinical alert issued previously for the node-negative breast cancer trials, Dr. Friedman stated that an attempt was made to improve the mechanics for writing and publishing the clinical update. To that end, he said, the update materials were submitted for review in early stages of development to the President of the American College of Surgeons, PDQ Editorial Board, Dr. John Niederhuber and the DCT Board of Scientific Counselors, Dr. Korn, and the principal investigators of both the NCCTG and intergroup trials. Dr. Friedman thanked Ms. Susan Hubbard and Mr. J. Paul Van Nevel, Office of Cancer Communications, and Dr. Bruce Chabner, Director, DCT, for their assistance in this effort. Approximately 35,000 copies of the update were distributed--to all members of the American College of Surgeons, the Society of Colorectal Surgeons, and the PDQ directory file.

Assessing the impact of the update issued on May 4, 1989, Dr. Friedman stated that the Drug Management Authorization Section of CTEP has received almost 7,000 physicians' inquiries and 1,000 requests for the protocol. In addition, 1,500 patients were registered to receive the drug under a group C protocol, and another 635 received the drug as a special exception. A large number of requests also were received from patients with either metastatic or Dukes' A disease. Dr. Friedman pointed out that the number of patients taking the drug represents 25 to 30 percent of all Dukes' C patients in the United States, a significant number in a situation where, previously, there was not thought to be effective therapy.

In describing followup strategies, Dr. Friedman reported that three studies are ongoing in the extramural community, which were designed in collaboration with CTEP's Investigational Drug and Clinical Investigations Branches and the Biological Response Modifiers Program (BRMP) and Clinical Oncology Program (COP). All include 5-FU and levamisole as a standard arm. There are no untreated, observation-only arms for patients with Dukes' B2 and C patients, in accordance with the views of both the investigators and the NCI. The studies are examining combinations of 5-FU modulated with folinic acid, leucovorin, or combinations of levamisole and leucovorin in different doses, schedules, intensities, and durations of therapy. Dr. Friedman remarked on the size of the studies (between 1,800 and 2,700 patients), which will make it possible to detect survival differences in the 10 percentage point range; furthermore, accrual will be completed in 2 to 3 years. Study options for the future include combinations of alpha-interferon and 5-FU and PALA and 5-FU, as well as other ways of maximizing the effect of levamisole.

Dr. Friedman provided the following information in response to questions:

- Patients registered to the group C protocol, which is a treatment activity, meet requirements for the research protocol but have declined to participate in a clinical trial.

- The FDA and CTEP have approved the group C protocol for Dukes' C disease only. The use of this agent for anyone other than recently resected Dukes' C patients has been discouraged.

- Special exemptions are granted for patients whose surgery predated beginning of levamisole therapy by more than the 5 weeks prescribed in the research protocol.

- No scientific data (e.g., survival curves) will be generated from the treatment activities (group C protocol and exemptions).

SCIENCE IN COOPERATIVE GROUP TRIALS

To introduce this topic, Dr. Friedman pointed out that cooperative groups frequently have been recognized for their ability to generate useful clinical trials data but their ability to perform laboratory investigation are less well known. He stated that he would demonstrate the ways in which correlative studies are being done within the group system and how that activity can be increased in the future. Using data gathered by the Clinical Investigations Branch of CTEP from all ongoing cooperative group clinical trials with laboratory correlates, he showed that there are laboratory correlates in 128 of the large studies distributed across the cooperative groups. A majority of studies in some groups (e.g., NSABP) have laboratory correlates integral to the clinical trial; many diseases are evaluated (solid tumors as well as hematologic malignancies); and modern laboratory investigation techniques are being utilized.

Dr. Friedman stated that CTEP is exploring ways to assess the impact of incorporating laboratory science with cooperative group activities and link the cooperative group program to the cancer centers program. Problems encountered include adapting present mechanisms, which are funded to perform clinical trials, to include enhanced funding for laboratory studies and supplementing scientific expertise in CTEP and the NCI review committees.

FUTURE PLANS

Dr. Friedman stressed the uniqueness of the cooperative groups and their value as a resource for future studies as well. He then described CTEP initiatives for the coming year, which included (1) development of a 5-year plan to set priorities for allocating limited resources in a time of unprecedented scientific opportunities and (2) conducting surrogate endpoint research. Emphases in setting research and funding priorities will be on linkage of laboratory and clinical studies, accrual issues, minority and aging population issues, specific diseases, drug development in the cooperative group system, modality development, national resource issues, and increased interaction among divisions and with cancer centers. Two topics to be examined in the second initiative are the relationship between disease-free and overall survival (in colon cancer studies first and other diseases later) and the relationship between clinical complete and pathologically complete responses and overall survival. Dr. Friedman pointed out that answers to these questions would have substantial implications for future approval of NDAs. He concluded by emphasizing that CTEP's preeminent problem is providing support for clinical investigation, not only to increase accrual to studies, but also to ensure that special scientific opportunities can be exploited to gather the maximum amount of information.

In response to questions, Dr. Friedman provided the following information:

- Cooperative groups recognize the need for strict quality control in laboratory studies and are dealing with the issue in many ways (e.g., having a central laboratory for all specimens).

- Funding is the limiting factor in incorporating laboratory studies. New sources of support are being explored (e.g., linkage with the interests of other NCI divisions), and some groups have agreed to reallocate internal resources.

- While the effect of the clinical update on accrual has not been studied, intergroup leaders and Dr. Moertel have conveyed to CTEP that they anticipate an increase due to the fact that every patient is offered an active treatment option; there are no observation-only arms.

- Ideas for incorporating laboratory studies have come principally from cooperative group members; however, CTEP does have established criteria that proscribe involvement in developmental work. Techniques proposed to be used should have a publication record and independent confirmation in other laboratories. Extramural and intramural experts are called on to assist CTEP in the review of proposals.

- Investigators now are informed of the set of conditions that may prompt a decision to stop a trial prematurely. Clinical trial methodology of the past few years include statistical sections that help to formulate rules (e.g., relating to interim analyses, thresholds) that are agreed upon in advance by all participants.

To answer a question as to whether CTEP ever specifies that a laboratory component must be incorporated in a particular study or type of study, Dr. Friedman reviewed the usual procedures followed in generating clinical studies. These involved extensive interaction in the planning stage among CTEP staff, group leaders, protocol-generating committees, interested investigators and laboratory personnel, and related experts. He noted that CTEP is beginning to understand the relationship of clinical trials to the larger oncologic investigative community and how to interact to realize the full potential of clinical trials. He concluded by stating that many more ideas and interested investigators exist than can be funded.

In anticipation of the overview workshop on clinical trials scheduled for January 31, 1990, Dr. Broder asked Board members to be thinking about how NCI can work to accommodate and respond to various, sometimes competing, needs in clinical trials.

XV. REPORT OF THE SUBCOMMITTEE ON PLANNING AND BUDGET-- DR. LOUISE STRONG

Dr. Strong called attention to the minutes of the subcommittee meeting, which summarized Dr. Broder's presentation on the FY 1991 President's Budget. It is proposed that NCI receive a 3.9 percent overall budget increase--a 7 percent increase for AIDS and a 3.6 percent increase for cancer. She noted that the subcommittee focused much of its discussion on the budget as it will relate to research project grants. The budget provides a 4.8 percent increase for research project grants, and in keeping with the NIH policy of maintaining a certain number of grants, noncompeting grants would have to be negotiated downward by 4 percent and competing grants by 20 percent. The budget for cancer centers is nearly flat, although the 1990 Senate Appropriations Committee report included a statement calling for the retention of the existing number of centers.

The first draft of the NCAB's biennial report was reviewed by the subcommittee. A revised draft of the report that incorporates comments of the subcommittee will be circulated to the full Board by the end of February.

The report of the Subcommittee on Planning and Budget was approved unanimously.

XVI. REPORT OF THE SUBCOMMITTEE ON AIDS--DR. LOUISE STRONG FOR DR. HOWARD TEMIN

Dr. Strong reported that the subcommittee heard an interesting presentation by Dr. Thomas Waldmann on creative genetic engineering approaches to the development of new therapies for AIDS patients. Discussion focused on ways of using transfected mutants of the specific HIV genes in new therapies and the technical difficulties of maintaining lasting expression of the transfected genes *in vivo*. Other topics for discussion included the 7 percent increase for AIDS in the 1991 President's Budget, which represents an escalation more in line with other disease entities, and the provision for 93 new AIDS full-time equivalents (FTEs) in 1990 and 15 in 1991. Dr. Strong said the subcommittee felt that it was important that NCI receive a portion of the

$20 million in NIH's AIDS construction-fund pool for AIDS construction at the Frederick Cancer Research Facility.

The report of the Subcommittee on AIDS was approved unanimously.

XVII. OFFICE OF TECHNOLOGY ASSESSMENT (OTA) STUDY OF ALTERNATIVE TREATMENTS AND IMMUNOAUGMENTATIVE THERAPY-- DR. ROGER HERDMAN

As introduction, Dr. Roper said that Dr. Herdman had been invited to discuss a 3-year OTA study of unconventional or alternative therapies and the work of a subcommittee that is endeavoring to develop a protocol for the assessment of alternative therapies. The first alternative therapy to be the subject of such a protocol is the immunoaugmentative therapy developed by Dr. Lawrence Burton. Dr. Roper explained that Dr. Herdman had been invited to speak because of continued interest in the topic and because of a recent increase in congressional interest in having NCI test immunoaugmentative therapy.

Dr. Herdman described OTA as a support agency of the U.S. Congress that prepares reports on science and technology at the request of congressional committees. OTA staff gather and synthesize information with the assistance of outside experts as needed and present options, not recommendations, to Congress.

Dr. Herdman said that OTA had received letters signed by 42 members of Congress expressing concern about the closure of the Burton Immuno-Research Center in the Bahamas and asking OTA to evaluate immunoaugmentative therapy. By law, OTA must respond to specific requests from committee chairmen or ranking minorities or both or members of its Board, so in consultation with Chairman John Dingell of the Energy and Commerce Committee, it was decided that OTA would study unconventional cancer treatments as a generic issue and also try to respond to the concerns about Dr. Burton. OTA's objective was to prepare a specific protocol for evaluating Dr. Burton's immunoaugmentative treatment, and, if such a protocol were to be implemented, to retain oversight authority if Congress and the principal investigator agreed.

Dr. Herdman stated that the first step in the effort had been to gather as much information as possible about Dr. Burton and his treatment. He acknowledged the cooperation of NCI and the FDA in this endeavor. Dr. Burton's treatment involves the repeated injections of fractions of blood from normal individuals into cancer patients according to a proprietary, computerized schedule, for the purpose of boosting the immune response to cancer. The treatment is given over the course of several months at Dr. Burton's clinic in the Bahamas and for a number of years thereafter, as needed. Dr. Herdman said OTA had not found any confirmation of Dr. Burton's results in the scientific literature.

OTA has attempted to negotiate certain aspects of an evaluation trial with Dr. Burton, i.e., that the trial would be conducted in the United States, the material would be prepared under good manufacturing practices, there would be regular medical supervision of the trial by an experienced clinical investigator, Dr. Burton could keep his computerized protocol secret, and there would be no requirement for animal testing of the material. Dr. Herdman said it was later decided that the trial would have to be done under an investigational new drug exemption. Negotiations are still in progress about the tumor type to be studied.

Dr. Herdman said that records of peritoneal mesothelioma cases, which Dr. Burton believes represent his most promising results, have been examined and these patients do have longer survival than the mean survival reported in the literature. Most of these patients went to Dr. Burton's clinic after receiving conventional treatment in the United States and were already experiencing a longer survival than the mean. Most patients had a tissue diagnosis of diffuse peritoneal mesothelioma made at accredited institutions in the United States.

The OTA report on unconventional cancer therapy is expected to be released in June, and Dr. Herdman offered to provide a draft to NCAB for review. He also offered to provide copies to anyone willing to formally review the document. The report will describe treatments, how they are accessed, the results, legal and financial aspects, and suggestions for evaluation. Dr. Herdman contended that the public and congressional interest in unconventional cancer treatment relates to the lack of effective therapy for many cancers, the danger and pain of many treatments, the fear of the results even with treatment, and the search for hope, caring, psychological support, and control of one's life.

With respect to evaluation of unconventional treatments, Dr. Herdman suggested the best-case review as a likely first step and enumerated the following principles, which would apply to the conduct of a trial in the United States: (1) practitioners should be involved in defining the parameters of the evaluation; (2) the principal investigator should not be associated with the treatment in any way; (3) the trial should take place in an accredited medical institution in the United States after review by an institutional review board; (4) an investigational new drug exemption must be obtained for treatment materials; and (5) the trial should be carefully designed to be as informative as possible. He further suggested that there are formidable informal barriers to evaluating unconventional cancer treatments and that persons working in the unconventional cancer treatment community are not knowledgeable about the bureaucracy or about evaluation methodologies and the design of clinical trials. Dr. Herdman stated his view that NCI had not facilitated evaluation of unconventional treatments by best-case reviews or other approaches.

In response to Dr. Korn's question about how to judge whether a therapy warrants formal evaluation given finite resources, Dr. Herdman suggested that NCI offer help in defining the evidence needed to document effectiveness of a therapy through a best-case review or other approach. Dr. Broder stated that for immunoaugmentative therapy, NCI had, in fact, offered to perform best-case reviews on a number of occasions and had arranged for a nongovernment employee to go informally to Dr. Burton's clinic to develop a plan for such reviews; but that undertaking was not successful.

Dr. Herdman reported that Representative Gary Ackerman had asked him to convey his sincere and serious concerns and his request that NCI make further efforts to facilitate an evaluation of immunoaugmentative therapy.

Points raised in discussion included the following:

- Testing of Dr. Burton's material has revealed contamination with HIV and hepatitis B virus.

- Dr. Burton refuses to reveal the composition of his material.

- NCI tests material from a wide variety of sources, e.g., the Natural Products Program, but requires that the source of the material be known, that the material be in a relatively pure form, and that antitumor activity be demonstrated in some test system.

- To proceed with an evaluation of immunoaugmentative therapy would require that Dr. Burton provide best cases for review, along with information on tumor biology, tumor progression or regression, and followup information including repeat scans and pathology.

- There is a small number of cancer patients who survive far beyond the expected mean survival and some who survive even without therapy.

- NCI has a process for examining reports of objective regressions, including in some cases where conventional therapy has not been used.

Dr. Broder pointed out that NCI must operate under established rules and regulations, and he asked for assistance in finding ways to improve the communication of information about NCI's mission in the context of these rules and regulations. Dr. Bettinghaus suggested that a public document be developed describing the attempts by NCI and others to work out arrangements for evaluating immunoaugmentative therapy.

Mrs. Brown noted that the American Cancer Society produces public documents on almost all unconventional therapies and is in the process of updating the document on immuno-augmentative therapy. All of the statements are published in *CA* and include an overview, history, and assessment of the evidence of efficacy. Mrs. Brown also stated that ACS recently conducted a survey on the extent of the problem of the use of unproven methods and found it to be very small: perhaps 6 to 8 percent of patients use unproven methods, but most also receive conventional therapy. Dr. Herdman said that this information would be included in the OTA report.

XVIII. BOARD OPERATING PROCEDURES AND NEW BUSINESS--MRS. BYNUM AND DR. KORN

Mrs. Bynum called attention to several information items provided to the Board: NIH and ADAMHA policy statements on nonexclusion from clinical trials of defined groups or subsets of the population for other than trial endpoint reasons; the final revised guidelines for comprehensive cancer centers; the guidelines for competing renewal applications for outstanding investigator grants (OIGs); and manual issuance 4513 describing board and council operating procedures. In response to a question about evaluating the OIG mechanism, Mrs. Bynum said it is probably too soon to know whether the goals of the program are being met but that applications for renewal will be structured to get information needed for a full-scale evaluation.

With respect to manual issuance 4513, Mrs. Bynum said that at the start of each calendar year, board operating procedures must be reviewed and approved. She noted that as a result of recommendations from the Agenda Subcommittee Working Group, some new procedures have been implemented so that the Board is now operating at a level close to the legal minimum. It is legally required that every summary statement be read by several knowledgeable members of the Board. Mrs. Bynum also drew attention to a listing of activities and negotiating authorities that the Board has delegated to the Grants Administration Branch. She requested and received the Board's concurrence with these procedures. (A quorum was not present.) Dr. Gray will contact Board members by mail to verify the assignment of program areas.

Following up on Dr. Bettinghaus's suggestion, Board members urged that NCI write up a case study of its actions with respect to immunoaugmentative therapy and submit it to OTA for inclusion as an appendix to its report. Dr. Broder asked Dr. Roper to write such a document, which will be provided to the Board for review before submission to OTA. He also emphasized that attention needs to be given to disseminating information about progress in cancer treatment.

In response to Dr. Mihich's question about the requirement for training graduate students in research ethics published in the December 22 issue of the *NIH Guide for Grants and Contracts*, Mrs. Bynum offered to obtain information on the current NIH policy with regard to training awards.

XIX. ADJOURNMENT--DR. KORN

There being no further business, the 73rd meeting of the National Cancer Advisory Board was adjourned at 4:14 p.m., January 30, 1990.

March 27, 1990
Date

David Korn
Dr. David Korn, Chairman