

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Dental and Craniofacial Research

National Advisory Dental and Craniofacial Research Council

Summary Minutes

Date: January 25-26, 1999

Place: Building 45, Conference Room E1&2
National Institutes of Health Bethesda,

Maryland 20892

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

MINUTES OF THE
NATIONAL ADVISORY DENTAL AND CRANIOFACIAL RESEARCH COUNCIL

January 25-26, 1999

The 157th meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on January 25, 1999, at 8:51 a.m., in Building 45, Conference Room E1&2, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:51 a.m. to 5:30 p.m., followed by the closed session for consideration of grant applications from 9:00 a.m. on January 26, 1999, until adjournment at 2:00 p.m. Dr. Harold C. Slavkin presided as Chair.

Members Present:

Dr. Judith E. N. Albino
Dr. John F. Alderete
Dr. Ernesto Canalis
Dr. D. Walter Cohen
Dr. Dominick P. De Paola
Dr. Caswell A. Evans, Jr.
Dr. Jay Alan Gershen
Dr. Marjorie K. Jeffcoat
Dr. E. Dianne Rekow
Colonel Michael P. Rethman
Dr. John D. Rugh
Dr. Martha J. Somerman
Dr. Everett Vokes

Members of the Public Present:

Dr. James Bader, Visiting Senior Fellow, Agency for Health Care Policy and Research, and
Professor, Sheps Center, University of North Carolina, Chapel Hill
Dr. Richard Carr, American Association of Dental Schools (AADS), Washington, D.C.
Dr. Aida A. Chohayeb, Professor, School of Dentistry, Howard University, Washington, D.C.
Dr. Joseph Ciardi, Consultant, Bethesda, MD
Dr. Robert J. Collins, Deputy Director, American Association for Dental Research (AADR) and
International Association for Dental Research (IADR), Alexandria, VA
Dr. Richard Green, American Dental Association, Washington, D.C.
Dr. R. Hart, Strategic Sciences, Inc., Rockville, MD

Dr. Cynthia E. Hodge, President, National Dental Association, Washington, D.C.
Mr. Scott Litch, AADS, Washington, D.C.
Ms. Gina Luke, AADS, Washington, D.C.
Dr. Frank Macrina, Chair, Board of Scientific Counselors, and Director, Institute of Oral and Craniofacial Molecular Biology, Virginia Commonwealth University, Richmond, VA
Dr. Stanley B. Peck, American Dental Hygienists Association, Washington, D.C.
Dr. Eli Schwarz, Executive Director, AADR and IADR, Alexandria, VA
Dr. Lawrence Tabak, Center for Oral Biology, University of Rochester, New York
Dr. Richard Valachovic, Executive Director, AADS, Washington, D.C.

Federal Employees Present:

National Institute of Dental and Craniofacial Research:

Dr. Bruce Baum, Chief, Gene Therapy and Therapeutics Branch, Division of Intramural Research (DIR)
Ms. Carolyn Baum, Committee Management Specialist and Council Secretary, Office of Science Policy and Analysis (OSPA)
Dr. Henning Birkedal-Hansen, Scientific Director, NIDCR, and Director, DIR
Dr. Norman S. Braveman, Chief, Program Development Branch (PD), Division of Extramural Research (DER)
Ms. Carol M. Beasley, Chief, Human Resources Management Branch, Office of Administrative Management (OAM)
Dr. Patricia S. Bryant, Director, Behavior, Health Promotion, and Environment Program, PD, DER
Ms. Sharrell S. Butler, EEO Manager
Ms. Joy Chambers, Grants Technical Assistant, PD, DER
Dr. Lois K. Cohen, Director, Office of International Health (OIH)
Dr. James Corrigan, Evaluation Officer, OSPA
Mr. George J. Coy, Chief, Financial Management Branch, OAM
Mr. Kevin Crist, Grants Management Specialist, Grants Management Section (GMS), Program Operations Branch (PO), DER
Dr. Scott Diehl, Acting Deputy Chief, Oral Health Promotion, Risk Factors, and Molecular Epidemiology Branch (OHPRFMEB), DIR
Dr. Raymond Dionne, Acting Chief, Pain and Neurosensory Mechanisms Branch, DIR
Ms. Yvonne H. du Buy, Executive Officer and Chief, OAM
Ms. Brenda Farmer, Secretary, Office of Communications and Health Education (OCHE)
Ms. Carla G. Flora, Chief, Information Technology and Analysis Branch (ITAB), OCHE
Ms. Christen Gibbons, Computer Specialist, ITAB, OCHE
Dr. Sharon Gordon, Director, Office of Education, OD
Dr. Kenneth A. Gruber, Director, Chronic Disabling Diseases: Osteoporosis and Related Bone Disorders Program, PD, DER

Dr. J. Silvio Gutkind, Chief, Oral and Pharyngeal Cancer Branch, DIR
Dr. Kevin Hardwick, International Health Officer, OIH
Dr. H. George Hausch, Chief, Scientific Review Branch, PO, DER
Ms. Deane K. Hill, Computer Programmer, Planning, Evaluation, and Legislation Branch
(PELB), OSPA
Ms. Lorraine Jackson, Diversity Program Specialist, and Co-Director, Diversity Programs, DER
Mr. LeVale Jenkins, Grants Technical Assistant, PD, DER
Ms. Susan Johnson, Acting Director, OCHE
Dr. Dushanka V. Kleinman, Deputy Director, NIDCR, and Executive Secretary, NADCRC
Dr. Eleni Kousvelari, Director, Biomaterials, Biomimetics, and Tissue Engineering Program, and
Director, Infectious Diseases: AIDS Program, PD, DER
Ms. Wendy A. Liffers, Director, OSPA
Dr. James A. Lipton, Special Assistant for Training and Career Development, DER
Dr. Jack London, Special Assistant to the Director, DIR
Ms. Mary Eileen Lukes, Computer Assistant, ITAB, OCHE
Dr. Dennis F. Mangan, Director, Infectious Diseases Program, PD, DER
Mr. Richard Marsophia, Grants Technical Assistant, PD, DER
Dr. J. Ricardo Martinez, Director, DER
Dr. Ann Miller-Chisholm, Staff Scientist, OHPRFMEB, DIR
Mr. Daniel Milstead, Grants Management Specialist, GMS, PO, DER
Dr. Edward Rossomando, Technology Transfer Program Director, OD
Dr. Joyce Reese, Technology Transfer and SBIR/STTR Administrative Program, PD, DER
Dr. Pamela Gehron Robey, Chief, Craniofacial and Skeletal Diseases Branch, DIR
Dr. Martin Rubinstein, Chief, GMS, PO, DER
Dr. Ann L. Sandberg, Director, Neoplastic Diseases Program, and Director, Comprehensive
Centers of Discovery Program, PD, DER
Dr. Harold C. Slavkin, Director, NIDCR
Dr. Judy A. Small, Director, Inherited Diseases and Disorders Program, PD, DER
Ms. Eileen Teng, Grants Management Specialist, DER
Dr. Sharon Wahl, Chief, Oral Infection and Immunity Branch, DIR
Ms. Anne Welkener, Grants Financial Analyst, GMS, PO, DER
Ms. Dolores Wells, Program Analyst, PELB, OSPA
Ms. Nora Winfrey, Secretary, DER
Ms. Mary Ann Williamson, Computer Specialist, ITAB, OSPA
Ms. Susan Wise, Program Analyst, PELB, OSPA
Dr. G. Wayne Wray, Chief, PO, DER
Dr. Kenneth Yamada, Chief, Craniofacial Developmental Biology and Regeneration Branch,
DIR

Other Federal Employees:

Dr. Wendy Baldwin, Deputy Director, Office of Extramural Research, Office of the Director
(OD), NIH
Dr. John Chao, OD, NIH

Dr. Priscilla B. Chen, Center for Scientific Review (CSR), NIH
Dr. Milton J. Hernández, National Institute of Allergy and Infectious Diseases, NIH
Dr. Daniel F. McDonald, CSR, NIH
Dr. John Norvell, National Institute of General Medical Sciences, NIH
Dr. John Storz, Army Dental Corp, U.S. Army, Falls Church, VA
Dr. Jane Steinberg, National Institute of Mental Health, NIH
Dr. Francis W. Wang, Dental and Medical Material Group, Paffenbarger Research Center of the
ADA Health Foundation, National Institute of Standards and Technology, Department of
Commerce, Gaithersburg, MD

OPEN PORTION OF THE MEETING

I. CALL TO ORDER AND WELCOMING REMARKS

Dr. Harold C. Slavkin, Director, NIDCR, called the meeting to order, welcoming all attendees to the 157th meeting of the Council. He invited all attendees to introduce themselves.

II. APPROVAL OF MINUTES

The minutes of the Council's meeting on October 15-16, 1998, were considered and unanimously approved.

III. FUTURE COUNCIL MEETING DATES

The following dates for future Council meetings were confirmed:

May 24-25, 1999
September 27-28, 1999
January 20-21, 2000
June 8-9, 2000
September 21-22, 2000

IV. REPORT OF THE DIRECTOR

Dr. Harold C. Slavkin, Director, NIDCR, commented on the challenges confronting dental research for the 21st Century. In his remarks, he focused on two main issues that were later addressed by the Council: genomic medicine and dentistry, and preparation of scientists to perform basic, translational, clinical, and health services research. Dr. Slavkin's written Director's Report to the

NADCRC was sent previously to the Council members and is appended to these minutes as Attachment III.

Dr. Slavkin noted that, as the new millennium approaches, the U.S. research enterprise is clearly poised to make "almost unimaginable" contributions in the 21st Century, characterized by many as "the biotechnology century." Two major areas of opportunity are genomics and informatics, coupled with clinical research. Dr. Slavkin asked the Council to entertain three questions in this regard: (1) How can we educate, train, and prepare laboratory, clinical, and behavioral scientists for genomic medicine and dentistry? (2) How can the dental community promote education and training that prepares these types of scientists to manage complex databases and to prepare for new ways of thinking about these knowledge databases (i.e., bioinformatics, computational biology, and the interface between biology and physics)? (3) What strategies are needed to prepare scientists for emerging scientific opportunities related to oral, dental, and craniofacial diseases and disorders in basic, translational, clinical, and health services research?

For consideration of the possibilities ahead, Dr. Slavkin asked, "What's in a face?" He noted that historical references to the face can be traced to Cicero who said, "everything is in the face." In the 19th Century, Robert Todd used the term "craniofacial," and Charles Darwin wrote The Expression of Emotions in Man and Animals, and, in 1912, Octave Crouzon published the first scientific paper using the term "craniofacial." Dr. Slavkin referred to the artist Chuck Close, who has captured the many dimensions of the face by reducing it to individual, textured pixels. The artist's approach is similar to that of biomedical researchers who seek to understand the complexity of the human body, including the face, by isolating discrete gene units. Indeed, NIDCR-supported scientists are analyzing the human face "gene by gene" and, in doing so, have already made major strides toward understanding the genetic aspects of craniofacial development.

Dr. Slavkin noted that new technologies (e.g., DNA microarrays) are being developed and applied to understand the "gestalt" of 20,000 or 50,000 genes at a time and, eventually, will be used to study the functioning of the entire genome in normal and abnormal situations. He noted that scientists expect to complete the entire genome for both the mouse and human by 2003. In the meantime, DNA, RNA, and protein databases are expanding at the rate of three genes a day, and the structure, function, and variability of genes and gene products are being reported in the scientific literature at a pace unheard of in human history. A good primer on the capabilities and promise of DNA chip technology has recently been published in the January 1999 supplement to Nature Genetics.

This basic research on the human genome has major implications for understanding and treating complex diseases, resolving developmental problems, and designing preventive and therapeutic drugs. Dr. Slavkin noted that scientists are combining principles of molecular biology with informatics, photo lithography, physics, engineering, biology, and clinical observation to advance technology rapidly from research to clinical application for individuals and, potentially, populations. In the intramural laboratories, for example, NIDCR scientists are utilizing this combination of approaches to develop biological datasets to study, for example, the stages of craniofacial development, the role of yeasts in disease, and the immune response of human cells.

Dr. Slavkin emphasized that, although the research agenda is moving forward, the "weak link" is the human link (i.e., the ability to be comfortable with the rate of change and the rate and complexity of new information). Scientists conducting laboratory, translational, clinical, behavioral, and health services research will need to be comfortable with the new idiom of biomedical research and to be able to engage in it and participate as appropriate. NIDCR training programs must address this need.

Other challenges also need to be addressed strategically in order to pursue the research agenda effectively. Some of the major challenges are: enhanced collaboration and partnerships among the Federal, public, and private sectors; dissemination of information technology and knowledge; promotion of science- or evidence-based clinical practice; clinical management of chronic diseases; understanding behavior-environment-gene interactions in complex diseases; international cooperation in clinical research; and stimulation of health promotion to reduce the burden of disease.

V. DIVISION OF INTRAMURAL ACCOMPLISHMENTS

Dr. Henning Birkedal-Hansen, Director, Division of Intramural Research (DIR), NIDCR, presented an overview of the Institute's intramural program and introduced brief presentations on each of DIR's seven branches. These presentations highlighted the mission and scientific accomplishments of each branch. Additional information can be obtained on the NIDCR home page (www.nidcr.nih.gov).

Introduction and Overview

Dr. Birkedal-Hansen spoke on the mission, science, people, and future of the intramural program. He noted that the Institute's intramural researchers have made remarkable discoveries over the past 50 years and have conducted significant scientific research during the 5 years of his tenure as director of the program. Through biomedical research, DIR supports the Institute's mission to improve and promote craniofacial, oral, and dental health through research. The intramural program emulates the model of an academic institution by supporting investigator-initiated research. Differing from extramurally funded research, the entire program is funded annually by the Institute and these funds are distributed to the investigators. Dr. Birkedal-Hansen noted that NIDCR and the extramural community benefit in two major ways by having an intramural program: the quality of the program "buys membership" in the NIH community, and the program provides access to the NIH clinical center, the largest U.S. hospital dedicated entirely to research.

DIR is structured to reflect major research themes, all of which relate directly to the Institute's mission. It comprises seven branches (see below), two units (Molecular Structural Biology, Functional Genomics), a Immunopathology Section, some core facilities, and the Office of the Scientific Director, which includes a newly created Office of Education. The staff of about 350 includes 40 independent investigators, 37 of whom are already tenured scientists and 3 of whom are

on tenure track. Dr. Birkedal-Hansen noted that DIR reflects the Institute's deep commitment to the support of research across the continuum of basic science, translational research, and clinical investigations. In FY 1998, for the first time, all DIR branches were engaged in both basic and clinical research.

Funding within the program has changed over the past 3 years, shifting from the funding of entire laboratories or branches to the funding of independent investigators based on annual budget negotiations. Accountability is assured by the Board of Scientific Counselors, which reviews each branch and investigator every 4 years to assess, retrospectively, research progress and funding, as well as future directions. On occasion, DIR also convenes informal, ad hoc external advisory groups to address particular research topics. Recent advisory groups have addressed clinical research, pain research, and emerging opportunities.

Training and mentoring opportunities abound within the program, which has about 120 of about 2,000 postdoctoral investigators at the NIH. DIR offers, for example, 3- and 5-year research training and mentoring programs for postdoctoral investigators and fellows; formal and informal clinical research training, including combination programs that lead to a Ph.D. or M.P.H. degree; an oral medicine training program that leads to specialty training and competency in clinical research; and a public health residency. DIR plans to expand these opportunities and to be able to offer a menu of customized clinical research training possibilities. In addition, DIR provides a research environment for students at local universities, participates in the 1-year program offered to dental and medical students by the Howard Hughes Medical Institute, offers a similar 1-year program for dental students, and participates in the NIH Clinical Center's 1-year Clinical Research Training Program. This year, DIR initiated a combined D.D.S./D.M.D.-Ph.D. program in collaboration with universities.

Other opportunities for students include DIR's Dental Student Award, a summer program that supports 10 to 12 dental students at the NIH each year; general student summer programs for all student levels, beginning with high school; a special students' program targeted to Hispanic and other underrepresented minority students; and ad hoc student programs created to meet individual's particular interests and needs. DIR also is developing a research training program for international students.

In closing, Dr. Birkedal-Hansen highlighted five priorities that will shape the program's future. These are: scientific emphasis on genomics, gene therapy, and biomimetics; expansion of clinical research and research training; partnerships with other NIH institutes and centers, particularly in the areas of bone diseases, pain, and head and neck cancer; improvement of the physical infrastructure and laboratory facilities; and recruitment of newly independent, tenure-track scientists to rejuvenate the program.

Craniofacial and Skeletal Diseases Branch

Dr. Pamela Gehron Robey, Branch Chief, noted that the mission of the branch is to determine the processes by which hard tissues are formed in health and disease states and, based on this knowledge, to develop new therapies to treat the variety of disorders that affect craniofacial and skeletal tissues. The research is focused on the cells, genes, matrix proteins, and minerals that compose hard tissues and is closely aligned with clinical observations. Branch investigators are focusing particularly on bone marrow stromal cells, a unique population of cells found in postnatal marrow. These cells are extremely important mediators of skeletal homeostasis, not only controlling bone formation throughout life, but also supporting hemopoiesis and giving rise to the cells that degrade bone. Branch investigators are trying to understand the sequence of events that occurs as these cells are directed into developing different phenotypes. Through this work, they have recently determined that the cells are a primary target of both genetic mutations and acquired changes.

Using the bone marrow stromal cells, investigators are also collaborating with the National Human Genome Research Institute on the Skeletal Genome Anatomy Project. They have sequenced more than 4,000 clones from different bone cell libraries and, so far, have identified about 40 genes that appear to be unique to bone formation. They are also studying the chromosomal localization of the various genes and are focusing on some novel genes to understand their structure and function. By constructing a microarray of skeletal-specific genes, the investigators will be able to examine different stages of differentiation and changes that occur in genetic and acquired diseases.

In addition, branch scientists are studying the function of extracellular matrices that are enriched in bone. Building on the isolation and characterization of decoran and biglycan, two proteoglycans that are highly enriched in bone, scientists have developed transgenic animals to study the function of these proteins and to better understand changes that occur in skeletal metabolism in disease states.

Basic findings are being translated into clinical applications. The branch has applied for approval by the Food and Drug Administration (FDA) to test the use of bone marrow stromal cells to regenerate bone in small animals. Use of these cells to treat more generalized diseases by injecting them into the circulation or through gene transfer and gene therapy is also being explored. The branch is also embarking on three clinical protocols to study and treat fibrous dysplasia in the NIH Clinical Center.

Craniofacial Developmental Biology and Regeneration Branch

Dr. Kenneth Yamada, Branch Chief, noted that the mission of this branch is to explore fundamental questions about the development and regeneration of craniofacial tissues, including molecular and cellular mechanisms of morphogenesis, organization of tissues, and cell differentiation. Branch investigators are identifying and characterizing genes that regulate the development and repair of craniofacial tissues and predisposition to cancer. New insights indicate that the mechanisms that regulate development overlap with those that regulate wound repair as well as tumor growth and metastasis. Scientists are therefore focusing on mechanisms of cell interaction and the regulation and control of these mechanisms.

Two proteins in the extracellular matrix that have received most attention are laminin and fibronectin. In studying these proteins, branch scientists have generated more than 700 overlapping peptides, some of which have biological effects. For example, certain peptides can promote or prohibit metastasis of tumor cells, promote differentiation of salivary glands, or promote angiogenesis and wound repair. These peptides are freely available to extramural researchers for study.

Branch scientists are specifically studying the responses of cell surface receptors to matrix molecules (e.g., integrins, growth factors), which can have important effects on biological processes. In one project, for example, scientists are studying the action of a new tumor suppressor protein, PTEN, which appears to affect the signaling pathway involved in a wide variety of human cancers, including head and neck cancer. In another project, the Oral and Craniofacial Genome Anatomy Project, scientists have begun to identify and characterize the expression of novel genes that affect craniofacial development. This work has led to the discovery of ameloblastin, a gene product linked to human amelogenesis imperfecta, and vinexin, a protein that appears to control cytoskeleton development.

In other projects, scientists are studying the responses of the genes for salivary gland cells to the extracellular matrix. The expression of genes at different stages of craniofacial development are of particular interest and are being studied in "knockout" mice.

Gene Therapy and Therapeutics Branch

Dr. Bruce Baum, Branch Chief, noted that the mission of this branch, since its inception in 1982, has been to understand the biology of salivary gland tissue and to address clinical problems related to the salivary glands. This work is focused on the two different epithelial tissues composing the salivary glands: acinar (water-permeable, secretory) cells, and ductal (water-impermeable, absorptive) cells. Through fundamental studies, researchers have sought to understand the activation of these cells by extracellular neuronal signals, the transduction of these signals, and the combined action of various ion channels and transport pathways to move salivary fluid.

The knowledge that has been gained from these basic physiology studies continues to be applied to the treatment of patients with salivary gland dysfunction. Branch scientists, for example, have developed the first and only drug, pilocarpine, approved by the FDA for treating salivary hypofunction.

Investigators are now pursuing clinical applications of gene transfer to correct inherited or acquired defects of the salivary glands. Using animal models and adenoviral vectors, they have achieved "proof of principle" on three fronts: transfer of a gene that encodes a water channel to stimulate secretion of fluid in irradiated salivary glands; transfer of a gene that encodes a biopharmaceutical to enhance secretion of a peptide to control mucosal candidiasis in the gastrointestinal tract; and transfer of a gene that encodes a biopharmaceutical to enhance secretion of a hormone into the

blood stream (systemically). Some of this important research involves collaboration with extramural scientists both inside and outside of dentistry.

In addition, branch scientists are making steady progress, in collaboration with other intramural and extramural scientists, to develop a first-generation artificial salivary gland. This work will particularly benefit patients who do not have any functioning salivary gland cells.

Oral and Pharyngeal Cancer Branch

Dr. J. Silvio Gutkind, Branch Chief, noted that cancers of the head and neck are one of the six most frequent malignancies worldwide. Each year in the United States, more than 29,000 new cases are diagnosed and result in more than 9,000 deaths. Very little is known about the molecular mechanisms involved in these cancers. Branch scientists are focusing on three aspects: the molecular mechanisms that control normal and aberrant growth, the molecular mechanisms specifically involved in squamous cell carcinogenesis, and development of animal models of squamous cell carcinogenesis.

In the first area, branch scientists are exploring how activation of receptors in cell membranes send signals through a network of kinases and second messengers, the expression of genes involved in these processes, and the relationship between the alteration of signaling molecules and cancer. In the second area, investigators are pursuing different approaches. Particularly exciting are attempts to clone dominant oncogenes, work that has led to identification of two different genes involved in squamous cell carcinogenesis. Other work is focused on the potential of introducing genes that regulate the growth of cells. In the third area, scientists are developing transgenic animal models to study, in vivo, the consecutive expression of oncogenes in epithelium. These models may also be useful for testing therapeutic approaches.

Recently, the branch has broadened its focus to include both translational and clinical studies. Two areas of emphasis are: identification of new molecules for the molecular diagnostics of head and neck cancer, and development of therapeutic approaches. Coincident with this expansion, the NIH established a new Inter-Institute Consortium in Head and Neck Cancer, in which the branch plays a leadership role. Two work groups have been organized under this consortium: the Head and Neck Cancer Genome Anatomy Project, and the Head and Neck Cancer Clinical Workgroup. In collaboration with colleagues at the National Cancer Institute (NCI), branch scientists are utilizing an NIH-developed laser microdissection technique to isolate cancer cells for gene studies. They have identified 39 novel genes involved in head and neck cancer, developed two cDNA libraries, and begun analyses of RNA samples by microarray.

In collaboration with NCI's developmental therapeutics program, branch scientists are developing new treatments for head and neck cancer. Two novel agents currently being explored are flavopiridol and UCNO1. To foster clinical studies of these and other agents, the scientists are helping to organize the first multidisciplinary NIH clinic for head and neck cancer. In all these efforts, NIDCR and other NIH intramural scientists collaborate extensively with extramural investigators.

Oral Health Promotion, Risk Factors, and Molecular Epidemiology Branch

Dr. Scott Diehl, Acting Deputy Branch Chief, noted that DIR's oral health promotion program has been moved to the Office of the Director, NIDCR, and that the branch now focuses specifically on molecular epidemiology. All of the research conducted by branch scientists is clinical research, except for some basic studies to develop molecular assays and perform statistical analyses. The mission of the branch is to combine family and population-based epidemiology strategies with use of the most advanced genomic molecular tools to identify and distinguish hereditary and environmental causes of dental, oral, and craniofacial diseases. The principal diseases currently emphasized include cleft lip and palate, head and neck cancers, and early- and adult-onset periodontal diseases. Other studies focus on susceptibility to tobacco addiction and the genetic basis for pain perception and response.

Dr. Diehl remarked that the field of molecular epidemiology has been revolutionized by the use of new statistical strategies that suggest that the association approach may be much more powerful than linkage analysis for understanding the genetics of common, complex diseases. Under ideal circumstances, for example, only 394 families might be needed to detect a gene, using an association approach, compared with 11,900 families needed for linkage analysis. This new understanding has stimulated major initiatives throughout the genetics research community to identify and characterize genetic polymorphisms.

Branch investigators are applying the association approach to examine the genetic variants of early-onset periodontal disease. Using this approach, investigators have been able to detect a greater number of candidate genes that may increase susceptibility to this disease. They are also exploring opportunities for collaboration to utilize NIDCR data sets for demonstration projects to study genetic polymorphisms. Investigators are also applying this approach to study the genetic and environmental contributors to nasopharyngeal cancer. This study is being conducted in collaboration with the NCI and scientists in Taiwan. The investigators will soon begin analysis of approximately 320,000 genotypes that have been assayed from more than 1,000 blood samples obtained from 173 Taiwanese families with multiple incidences of this disease.

Pain and Neurosensory Mechanisms Branch

Dr. Raymond Dionne, Acting Branch Chief, noted that pain is prevalent in patients with most disease. Statistics indicate that pain is a major symptom in approximately 75 percent of patients with advanced cancer, is experienced by 30 to 80 percent of patients infected with the human immunodeficiency virus (HIV), and is severe and unrelieved in up to 40 percent of patients at the end of life. Current treatments for pain (e.g., nonsteroidal anti-inflammatory drugs) can be improved; many are thought to be associated with hospitalization and even death.

The NIDCR has played a dominant role in NIH-supported intramural pain research over the past four decades. The research paradigm of the current branch is grounded in basic studies of pain mechanisms in animal models, translational studies of research concepts in humans, and clinical trials to test new analgesics. In basic studies of the molecular and genetic mechanisms of pain, branch scientists have developed nocitoxins which selectively inactivate pain pathways, demonstrated the use of a viral vector for neuronal gene therapy in animals, shown that plasticity in the nociceptor pathways following persistent neonatal pain in animals results in changes that persist into adult life, and elucidated the molecular basis for gender differences in pain. They are continuing research in these areas and are identifying novel genes associated with pain.

Using positron emission tomography, the scientists have been able to image pain in the central nervous system of active, aware subjects. With this ability, they are studying the effects of acute pain on the sympathetic nervous system, the effects of persistent pain conditions on plasticity in the central nervous system, the specificity of pain activation in the central nervous system, the diversity of acute pain and response to analgesic drugs, and relationship between chronic orofacial pain and failed temporomandibular implants. These studies are making it possible, for example, to quantify the variation in pain experience reported by patients who receive the same level of stimuli.

In parallel with these studies, the branch conducts a clinical research program for the NIH Pain Research Clinic which the branch helped establish more than 15 years ago. The types of studies undertaken include evaluations of novel receptor antagonists, blockade of central hyperalgesia, sites and mechanisms of *in situ* analgesia, mechanisms and treatment of persistent pain conditions, and genetic mechanisms of acute and chronic neuropathic pain. As a result of the uniqueness of the intramural program, branch scientists have been able to clarify the benefits of different pain-control procedures for patients undergoing oral surgery for a variety of conditions.

The clinical research program also provides a good environment for clinical research training. The branch has trained more than 30 postdoctoral fellows (anesthesiologists, dentists, and clinical psychologists) and supports as many as 10 active clinical protocols at a given time. Branch scientists have written a standard text, The Design of Analgesic Clinical Trials, and are developing a new training method based on the design of palliative care trials.

In closing, Dr. Dionne said that the NIDCR continues to be the lead institute for the NIH Pain Research Clinic and for the NIH Pain Interest Group. Also, for the past 15 years, the branch has operated the NIH Clinical Center Pain Consult Service. In the near future, the branch will help establish a new NIH-wide Pain Research Program, a new Clinical Center Pain and Palliative Care Service, and a new Anesthesia Research Fellowship Program.

Oral Infection and Immunity Branch

Dr. Sharon Wahl, Branch Chief, noted that the branch traces its roots to 1949, even further back than the Institute's pain research program. The branch focuses on infectious and parasitic diseases, which are the leading cause of death worldwide and the basis for many disease processes. The

mission of the branch is to understand infectious pathogens, host defense mechanisms, and pathogen and host interactions, and to consider therapeutic interventions.

One of the microorganisms of particular interest to branch scientists is HIV. Still a serious problem worldwide, HIV infects about 16,000 people each day and, in 1998 alone, infected nearly 6 million people. Although the mucosal surfaces are the major portal of HIV transmission, transmission through the oral mucosa is infrequent. However, HIV can be found in tissues around and in the oral cavity. Branch scientists continue to try to unravel this mystery.

A main hypothesis, set forth originally by Drs. Bruce Baum and Philip Fox, is that the oral cavity may contain one or more HIV inhibitors. The branch has focused on one inhibitor, secretory leukocyte protease inhibitor (SLPI), which is produced in the acinar cells of the salivary glands. Branch scientists have shown that SLPI binds to CD4 positive monocytes in T cells to inhibit HIV infection and that this action appears to take place very early in the life cycle of the virus (i.e., during entry or uncoating of the virus). Further studies conducted in the branch and other laboratories around the world show that SLPI not only has antiviral activity, but also has antiprotease, antibacterial, antifungal, and anti-inflammatory activity. SLPI appears to be an important part of a host's innate defense mechanisms and has been shown to be species-specific.

To probe the functions of this molecule, branch scientists have recently genetically engineered a "knockout" mouse missing the SLPI gene. They also have received approval and funding for a clinical trial to test SLPI as a potential treatment for delayed or defective wound healing. In closing, Dr. Wahl noted that the SLPI project, one of many in the branch's portfolio, reflects the strengths of the intramural program--the ability to conduct multidisciplinary basic research, to study diseases from a multifaceted approach, and to test preclinical findings in the clinic.

Discussion

The Council thanked the intramural staff for their overview of NIDCR's intramural research program. The Council remarked on the incredible progress that has been made in research on SLPI and asked about NIDCR efforts to obtain additional support for research on emerging infectious diseases. Dr. Slavkin noted that emerging and re-emerging infectious diseases is an area of opportunity identified for the NIH by the Administration and that the NIDCR will compete for any additional resources that become available.

The Council noted the importance of nutrition with regard to infection and asked about NIDCR's support for research on nutrition. Dr. Birkedal-Hansen said that the intramural program has had little strength and only minor involvement in nutrition research. Dr. Martinez said that the extramural program supports a number of activities that address nutrition, directly or indirectly, and that NIDCR is interested in developing support for this research as it relates to specific program areas (e.g., cancer, infectious diseases, chronic diseases). Staff noted that NIDCR supports research grants on the relationship of nutrition to NOMA and to periodontal and cardiovascular disease. In addition, NIDCR is developing an oral component that includes nutrition for the National Health and

Nutrition Examination Survey (NHANES IV) and is collaborating with the NIH Office of Research on Nutritional Supplements on an upcoming conference.

Dr. Lois K. Cohen, Director, Office of International Health, NIDCR, said that the interaction of nutrition and infectious disease is a strong part of the Institute's international collaborative research agenda. Research on the relation of nutrition to the development of craniofacial anomalies and to the prevention of cleft lip and cleft palate will be stimulated by two forthcoming Institute initiatives: a Request for Proposals to create and administer a multinational consortium for craniofacial birth defects, and a Request for Applications (RFA) for a prospective international, multicenter clinical trial of folate intervention to prevent recurrence of cleft lip with or without cleft palate. The Council approved the concept for these initiatives at its June 1998 meeting.

In closing, Dr. Birkedal-Hansen encouraged the Council to review the materials on the intramural program that are sent to members throughout the year, and he invited Council members to participate in the reviews conducted by the Board of Scientific Counselors.

VI. DIVISION OF EXTRAMURAL UPDATE

Dr. Ricardo Martinez, Director, Division of Extramural Research (DER), NIDCR, presented an update on DER activities. He gave an overview of DER's research portfolio and discussed scientific opportunities and challenges for the future.

Extramural Research Portfolio

In FY 1998, NIDCR spent approximately \$161 million on extramural research, an increase from approximately \$139.5 million in FY 1996. These monies were distributed among six scientific program areas: inherited diseases and disorders; infectious diseases; neoplastic diseases; chronic disabling diseases; biomimetics, tissue engineering, and biomaterials; and behavior, health promotion, and environment. Funding obligations increased in some areas and remained stable or declined slightly in other areas. Overall, the portfolio was relatively balanced, with support in all areas. In FY 1998, the number of projects (research grants and contracts) supported varied by area. Recent increases mostly reflected NIDCR initiatives (Requests for Applications, Program Announcements) to stimulate research in certain areas (e.g., neoplastic diseases, biomimetics, and infectious diseases, especially AIDS).

In FY 1998, NIDCR continued to emphasize investigator-initiated research project grants (R01s), which accounted for 70 percent of extramural expenditures, an increase from 67 percent in FY 1996. The success rate for research project grants was approximately 27 percent. Expenditures for research contracts and interagency agreements totaled \$6.5 million, an increase from \$6.3 million in FY 1997. Expenditures also increased for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards, from \$4 million in FY 1997 to \$4.2 million in FY 1998; many of these awards were under the

biomimetics, tissue engineering, and biomaterials program. In FY 1998, U.S. dental schools received approximately \$96 million in awards from NIDCR and close to \$26 million from other NIH institutes and centers, for a total of \$122 million. NIDCR also provided approximately \$31 million to U.S. medical schools.

Future Research Opportunities and Challenges

Anticipated developments in the extramural research portfolio are related to NIDCR's three strategic initiatives as outlined in the Institute's Strategic Plan: research opportunities, research capacity, and health promotion. Three major areas of research opportunity are: molecular medicine (e.g., dissection of the genetics of complex diseases, identification of biomarkers of disease); clinical research (e.g., fostering of clinical and molecular epidemiology, establishment of clinical trials networks) and health promotion research; and biotechnology and bioinformation infrastructure (e.g., discovery of biosensors, development of microarrays, development of cell and tissue repositories, patient databases, family registries).

Some of the areas of emphasis for FY 1999 and FY 2000 will be craniofacial anomalies (e.g., functional genomics research, molecular and clinical epidemiology); infectious diseases (e.g., genomes of different bacteria, international research partnerships); head and neck cancer (e.g., dysregulation of cell cycle, early detection and prevention, treatment outcomes); chronic disabling diseases (e.g., molecular genetics of autoimmune disease, oral health manifestations); and biomimetics, tissue engineering, and biomaterials (e.g., biomarkers and biosensors, cell and tissue resources).

The opportunities for developing research capacity are the same as in the Strategic Plan: enhanced training and career development programs, and development of physical and technological resources (including data bases and instrumentation). Well-trained personnel and appropriate resources, as well as cross-disciplinary teams and approaches, are needed for research on complex, multifactorial diseases.

The opportunities for health promotion, as suggested in the Strategic Plan, are to develop resources for promoting health promotion, to use science to promote health, and to analyze and respond to changes in health needs and disease trends. The challenges and issues we face relate to the continuous transfer of scientific advances into clinical care through translational research, health promotion, and health education.

Two major challenges over the next 2 to 3 years will be to strengthen DER's training activities (see section IX below) and its portfolio in clinical research and health promotion research. These efforts will be undertaken while maintaining DER's already strong portfolio in basic science and molecular medicine.

Discussion

In response to a question about awards to dental schools, Dr. Martinez said that the total amount of NIDCR funding has not changed significantly during the past 5 years, although the number and success of applications from investigators in dental schools to other NIH institutes and centers have increased. With regard to science transfer and health promotion, the Council suggested that NIDCR can be a tremendous leader in disseminating existing public health literature to community-based organizations that serve underrepresented minority groups.

Dr. Martinez noted that, because of the importance of science transfer and health promotion, DER will be converting the program area of behavior, health promotion, and environment to a separate office within DER. Dr. Dushanka V. Kleinman, Deputy Director, NIDCR, said that the Office of the Director, NIDCR, maintains a complete list of professional voluntary organizations, has created a network of organizations that participated in the previous Council meeting (October 1998), and is discussing interagency agreements with other agencies in the Public Health Service to accelerate science transfer and to identify opportunities for health promotion. In these collaborations, the NIDCR will focus on research aspects. Dr. D. Walter Cohen commented that one of the goals of the Friends of NIDCR is to bring information from research to the public. For example, in celebration of its first anniversary, the Friends of NIDCR is hosting a meeting of health writers on January 27 at the National Press Club to discuss the oral complications of cancer.

VII. FREEDOM OF INFORMATION ACT

Dr. Wendy Baldwin, Deputy Director, Office of Extramural Research, NIH, informed Council about the Omnibus 1999 Appropriations bill and the potential problems that this bill creates for the NIH. In this law, Congress directs the Office of Management and Budget (OMB) to amend OMB Circular A-110 to extend the Freedom of Information Act (FOIA) to "require Federal awarding agencies to ensure that all data produced under an award will be made available to the public under the [FOIA]...." The data that could be requested under this law include any data that are produced under any NIH-supported award, including research grants.

Dr. Baldwin said that the law has tremendous implications for everyone in the extramural research community. In response to Congress' direction, the OMB will soon be issuing a Notice of Proposed Rule Making in the Federal Register for a 60-day comment period. In anticipation of this notice, the NIH has prepared a draft document, "Implications of an Extension of the FOIA to Grantees Research Data" (1/19/99), which was distributed to the Council. This document will be revised, and revisions will be posted on both the NIH and NIDCR websites.

Dr. Baldwin stated that the NIH is a strong advocate for data sharing. The amendment to Circular A-110, however, will be particularly difficult for NIH and its grantees. The legislation fails to provide, for example, adequate definitions for various terms [e.g., what does "data" include (clinical trials data, videotapes, laboratory notebooks, etc.)]; clear assurances for confidentiality of patient information; elaboration on the timing and release of data (e.g., repeated requests for information could be disruptive to the research being conducted); clear protection of privacy and proprietary

data; distinction between "data that are produced in whole or in part by Federal funds," thus threatening potential collaborations with other funding sources; compensation for meeting FOIA requests; guidance on the full extent of time that data could be accessed (data analyses often continue far beyond submission of a final study report); procedures for assuring compliance by grantees, particularly previous grantees; and consideration of the administrative difficulties for the NIH and grantees.

Dr. Baldwin emphasized that the law fails to address a wide range of nuances particular to different research settings, projects, and data. As written, the law could disrupt many aspects of the research process, including research grants, research training, clinical investigations, recruitment and participation of patients in research protocols, international collaborations, and administration of NIH awards.

Dr. Baldwin said that Congressman George E. Brown, Jr., (D-CA) has introduced a bill (HR 88), which would appeal the law, and that a number of Representatives have signed a letter to OMB expressing concerns about the law. She encouraged Council members to review and comment on the present rule in response to the Federal Register notice. Comments on the particular concerns of different constituencies and communities, as well as constructive suggestions, would be most useful. The NIH has established a working group to identify specific issues of concern to the different institutes and centers and to suggest strategies for making implementation of the law manageable. The NIH will be submitting a comprehensive, inclusive NIH response to the OMB.

Discussion

The Council noted that the American Association of Medical Colleges has notified all medical school chancellors about the anticipated Notice of Proposed Rule Making, and the members suggested that the dental community contact dental school deans and dental researchers to encourage them to comment on the Federal Register notice.

VIII. PROPOSAL FOR A COUNCIL STUDY OF GENETICS AND ORAL, DENTAL, AND CRANIOFACIAL DISEASES AND DISORDERS

Dr. Dushanka V. Kleinman, Deputy Director, NIDCR, presented a proposal for a Council study of the Institute's portfolio in genetics and oral, dental, and craniofacial diseases and disorders. Preceding her presentation, and presented as background for the Council, Dr. Jane Steinberg, Acting Director, Division of Extramural Activities, National Institute of Mental Health (NIMH), NIH, described a similar study conducted by the NIMH and its Council.

Overview of the National Institute of Mental Health Council Study of Genetics

Dr. Steinberg said that the NIMH's Council study was undertaken as part of the Institute's planning process. With NIMH's reintegration into the NIH, this process has shifted from the development of

encyclopedic reports on broad research fields to more targeted attempts to understand research gaps and opportunities in specific program areas of the NIMH portfolio. The genetics and mental disorders area was selected as one of the first attempts because of the recognized need for new models of mental disorders, based on multiple and complex gene-environment interactions, and for sufficient resources to fund this research.

For the study, the NIMH convened a genetics workgroup consisting of a mix of researchers who were and were not already working on the genetics of mental disorders. The workgroup followed a combined planning and evaluation process that has been adopted by the NIMH for its program reviews. This process includes a review of the existing research portfolio; interviews with intramural and extramural staff; solicitation of comments from grantees, advocacy groups, and professional societies; presentations from representatives of different interests (e.g., the business, biotechnical, pharmaceutical communities); panels of new investigators; comments from research project officers; and an international forum. Through this process, the workgroup identified the research issues that needed to be addressed. For the genetics area, the issues included phenotype, sample size, replicability of findings, pool of researchers, and collaborative use of expensive and rare resources.

In its discussions, the workgroup highlighted several actions needed to build toward the future: improved use of existing resources, investment in collaborative research efforts, and cooperation with other NIH components to develop models of complex diseases. The workgroup set forth 22 specific recommendations grouped under the following six goals: create and analyze large, well-documented samples, foster collaborations, recruit and retain new researchers, sponsor initiatives to stimulate research on the molecular genetics of mental disorders, address administrative issues, and establish a genetics advisory group.

The planning process culminated in publication of the NIMH report Genetics and Mental Disorders (September 1997). Dr. Steinberg noted that the effort was significant for the NIMH in several ways: It "put our illnesses into play" within the genetics research community; helped demonstrate that identification of genes for disease susceptibility was not the endpoint, but just the beginning of understanding how genes work; suggested that understanding may come by "unbundling" the complexity of the disorders; showed that other NIH portfolios could be strengthened by NIMH involvement; helped establish research directions for the next 5 years; and fostered relationships with other NIH components.

Discussion. In response to questions, Dr. Steinberg said that NIMH is fostering recruitment and retention of researchers in a number of ways, such as making genetic data available, issuing program announcements on the secondary analyses of data, participating in cross-NIH training efforts in statistical modeling and molecular genetics, identifying individuals who have desirable technical skills, and funding short-term retraining courses that match highly productive researchers and utilize existing data bases.

Proposal for NADRC Study

Dr. Kleinman said that NIDCR has spoken with Dr. Steinberg about the NIMH study and proposes to establish a similar workgroup to assess NIDCR activities in genetics and oral, dental, and craniofacial diseases and disorders. Dr. Judy A. Small, Director, Inherited Diseases and Disorders Program, DER, NIDCR, will lead the workgroup. In response to Dr. Kleinman's invitation, four Council members indicated interest in participating in the planning and conduct of the study: Drs. Albino, Canalis, Cohen, and Rugh.

Dr. Kleinman said that the workgroup will review the Institute's current portfolio in genetics research, specify research gaps, identify opportunities for linkages with other NIH components, explore training and career development needs, critically review science transfer activities as they relate to the public and health care professionals, and address the social, legal, and ethical implications of the research. The workgroup's report is expected to be available for the Council's September 1999 meeting.

Linkage with the Council is an important component of the proposed study. Council members are invited to help identify workgroup members and to participate in the study, and the Council will be kept informed about the workgroup's deliberations.

Discussion. The Council emphasized the importance of engaging minority populations and communities in the initial stages of the study. Outreach through a variety of settings would help foster understanding of minorities' particular concerns about genetics research, consideration of the complex issues involved, and minorities' participation in these important discussions. The Council noted that education of the public about genetics research needs to be addressed by the entire science community and all NIH components.

IX. NIDCR BLUE RIBBON PANEL ON RESEARCH TRAINING AND CAREER DEVELOPMENT

Dr. James A. Lipton, Special Assistant for Training and Career Development, DER, presented an overview of the NIDCR Blue Ribbon Panel on Research Training and Career Development which the Institute will convene in spring or summer 1999. Following his remarks, Dr. Martinez introduced a panel of four experts who highlighted key issues in research training and career development. Dr. Martinez then invited Council's guidance on the planning of this effort. The purpose of the session was to develop agenda topics, establish a meeting date, identify potential participants, and determine the types of data needed for the Blue Ribbon Panel.

Overview: NIDCR Blue Ribbon Panel

Dr. Lipton commented on the timeframe for the panel, forces that impinge on research training and career development, possible discussion topics for the panel, and types of data that NIDCR can collect. He noted that, in order to complete the Institute's budget initiatives for FY 2000 and 2001 (which are due by the end of FY 1999) and to begin a new round of the Dentist Scientist Award

(DSA) program (by issuing an RFA at the end of FY 1999 or early in FY 2000), the Institute would like to receive the panel's draft report by October 1999 and its final report by January 2000.

Three basic forces are currently impinging on research training and career development: research environment issues, professional education issues, and the changing scientific directions for the 21st Century. Dr. Lipton noted that the NIH experienced a 30 percent decrease in first-time physician and dentist applicants for research grants from FY 1994 through FY 1997, the total number of physician postdoctoral trainees supported by the NIH has decreased by 51 percent since 1992, and the number of M.D.s applying for research grants decreased 57 percent from 1996 through 1998. In addition, many key senior positions in dental schools are not being filled and fewer dental students and oral health professionals are interested in research careers. Contributing factors include students' increased debt, the culture of dental education, faculty's lack of support for research, lack of role models and mentors, and a perceived lack of prestige or value for research. The changing scientific directions were addressed previously (see sections IV and V above).

Dr. Lipton suggested several discussion topics which the panel could consider. They concerned the main issues behind the three forces noted above, development of a workforce and training portfolio most responsive to the needs of science, assistance to help dentists become outstanding researchers, encouragement and development of excellent scientists from nondental backgrounds, improved communication to facilitate research and training at health science centers and universities, and life-long learning for researchers.

Dr. Lipton also noted some of the types of data that NIDCR could collect to support the panel. He showed data on the relationship between the background or training (degree received) of principal investigators and their participation in NIH-supported research; data on the history of individual and institutional DSA recipients; and number of T32 trainees, under the National Research Service Award (NRSA) program, by degree. In the first case, he noted that the NIDCR can provide the following: number of investigators submitting research project grant (RPG) or R01 applications, and number and success rates of investigators receiving RPG or R01 awards.

For individual versus institutional DSA recipients, NIDCR can provide the following: number and percentage who completed the DSA program, number submitting research applications to and receiving awards from the NIH, success rates by type of award received, number of NIH awards received by mechanism, number of years between completion of DSA program and first R01 award, dental schools attended, and current academic location. For NRSA recipients and career development awardees, NIDCR can provide the total funding and number of positions funded for each award. For NRSA recipients, NIDCR also can provide the percent and gender of minorities overall in institutional or short-term training programs. In all cases, data are available to show trends over time.

Discussion. The Council and staff noted that the following information may also be useful to the panel: additional data to more accurately portray the DSA program; data on the resources needed and provided by host institutions to nurture potential researchers (e.g., DSA recipients) and to

attract dental researchers (e.g., DSA graduates); case studies of institutions that have hired DSA graduates; data on the drop-out rate of DSA recipients (i.e., percent who do not complete the program or who drop out of a research); case histories of distinguished, life-long dental researchers who have been supported by the NIDCR; data on co-investigators who have received NIDCR support for research training; success rate of DSA recipients who received postdoctoral research training; and success rates of DSA recipients compared to non-DSA trainees. The Council also noted that debt forgiveness is a critical issue that the panel should address, and the Council suggested that grantees and program directors could provide information annually to help NIDCR update its data.

Key Issues: Research Training and Career Development

Four experts presented their perspectives on key issues in research training and career development.

National Institute of Allergy and Infectious Diseases (NIAID). Dr. Milton J. Hernández, Director, Office of Special Populations and Research Training, Division of Extramural Activities, NIAID, NIH, described NIAID's training portfolio, a new transition award, and NIAID efforts to attract minority scientists into its intramural laboratories. NIAID supports training grants and fellowships under the NRSA mechanism, career development (K) awards, and supplements for underrepresented minorities.

Last year, NIAID and several other NIH components instituted a Research Scholar Development Award (K22) for postdoctoral investigators moving to positions as assistant professors. This award provides transition, start-up funds for new investigators. It can be tailored (e.g., in duration and level of funding) to the needs of an NIH component; at some institutes, the K22 is solely an extramural award, while at others, it is both an intramural and extramural award.

At the NIAID, the K22 is an extramural, nonrenewable award for 2 years, and, during this pilot phase, is restricted to postdoctoral investigators who are in NIAID's intramural program or who are supported by NIAID training grants or fellowships. Applications are submitted by individuals, who do not have to have a sponsoring institution, and are reviewed in two phases. During phase I, applications are peer reviewed, and individuals are notified that they have been approved for funding based on their securing an assistant professorship within 1 year; after the individuals secure a position (phase II), NIAID staff conduct a followup review to ensure that the individuals will have sufficient time and support for research. The K22 provides \$150,000 in year 1 and \$100,000 in year 2, and salary is limited to \$50,000.

National Institute of General Medical Sciences (NIGMS). Dr. John C. Norvell, Assistant Director for Research Training, NIGMS, NIH, said that research training programs are a major part of NIGMS' mission. The Institute allocates about \$100 million to these programs; this support represents about one-third of all research training supported by the NIH and about one-half of all predoctoral training supported by the NIH. NIGMS supports seven predoctoral programs and, unlike other NIH components, they are broadly focused on the basic sciences, not on particular

disciplines. The programs foster multidisciplinary, interdepartmental research training. For the past 30 years, NIAID also has been supporting the highly successful Medical Scientist Training Program (MSTP) for individuals seeking a combined professional (e.g., M.D., D.D.S.)/Ph.D. degree. In addition, NIAID supports postdoctoral fellowships, a small postdoctoral training grant for clinical research, and various programs for minority students.

Dr. Norvell noted that a continuing issue for NIAID is in which fields research training should be offered. A major issue currently is whether to launch a new predoctoral, and possibly postdoctoral, program in bioinformatics. The research need for expertise in computational methods and bioinformatics, and the decrease in the number of students with adequate training in quantitative methods, have stimulated NIAID toward two actions: creating a new predoctoral training program in bioinformatics, which will include engineering and computational biology; and encouraging all institutional training programs supported by the NIAID to seek students with appropriate quantitative skills.

In addition, NIAID is addressing ways to broaden the MSTP. When re-announcing its training program recently, NIAID encouraged the institutional programs supported by NIAID to broaden the MSTP to include fields such as computer sciences, social and behavioral sciences, economics, and public health specialties.

Agency for Health Care Policy and Research (AHCPR). Dr. James Bader, Visiting Senior Fellow, AHCPR, and Professor, Sheps Center, University of North Carolina, Chapel Hill, spoke about research training programs for health services research. Dr. Bader directs the only dental health services research training award, which is "piggybacked" on a health services award at UNC and has supported training for two trainees. He highlighted several constraints of health services research in dentistry that should be considered when appointing the panel and selecting topics for consideration.

First, health services research in dentistry is a small enterprise consisting of no more than 30 researchers who are concentrated in a few institutions and are part-time. Second, recruitment of good students and dental health services researchers is difficult because of the lack of laboratory facilities, interesting research processes, and on-campus research opportunities. Much of the research involves entering data and making observations in remote practice environments away from campus. Third, qualified predoctoral students face several detriments to pursuing a career in health services research. Because of the nature of the research, 5-year grants to support a line of inquiry are not available; rather, separate grant applications, which are laboriously constructed, have to be prepared for each research question and then combated within study sections. In addition, involving pre- and postdoctoral researchers in ongoing projects is not feasible unless the projects are very large and are sustained by more than one research grant.

Dr. Bader noted that, because of these constraints, the opportunities for expanding training programs in dental health services research are limited unless fundamental aspects of this research are changed. This situation may also apply to dental research involving the behavioral sciences. Dr.

Bader cautioned that the term "clinical research" has different meanings in different settings (e.g., dental schools, health services) and will need to be defined by the panel.

In discussion, Dr. Bader argued that dental health services research would be conducted best by a collaborative dental research team in a multi-institutional setting, perhaps supported by a program project grant (PO1). He noted that health services research is becoming more complicated and requiring more training and that postdoctoral support is "what really makes it happen." He suggested that the Robert Wood Johnson Dental Services Research Scholars Program, which supported training during the 1980s, is a good model for training investigators who could join existing teams of dental health services researchers, but not for training independent researchers who could apply successfully for R01s.

University of Rochester. Dr. Lawrence Tabak, Senior Associate Dean for Research, and Director, Center for Oral Biology, School of Medicine and Dentistry, University of Rochester, New York, listed several key ingredients for successful research training and career development in the post-genomic era. These include the following: sufficient resources for recruiting potential researchers (which amount to about \$600,000 per recruit at the University of Rochester program); multidisciplinary, cross-department training in an academic health center; appropriate, high-quality training within creative training programs (e.g., the new K22 program); postdoctoral research training support; longer-term support for research faculty [e.g., the Method to Extend Research in Time (MERIT) award], which makes mentoring more feasible; support for selected, good training experiences and environments rather than broad support across many institutions; extension of training opportunities to nondentists (e.g., Ph.D.s); improvement of the D.D.S./Ph.D. program to the level of the MTSP (e.g., by enhancing its flexibility, involving dental school deans); and strengthening the research pipeline by interesting minority students in science as early as grades K-2.

In discussion, Dr. Tabak supported the concept of instituting an oral biology Ph.D. program in dental schools if the program is integrated with other university departments and encompasses modern science. The Council emphasized that one of the biggest impediments to research training in dentistry is students' lack of quantitative skills and that, when designing new models for training, consideration needs to be given to "plugging up" these gaps, as well as engaging students' interest in the early K-2 years.

Guidance from Council

Dr. Martinez invited the Council to comment on the date, membership, and agenda topics for the Blue Ribbon Panel. The Council noted that research training and career development of scientists is an exceedingly complex problem that requires a holistic approach and the collaboration of multiple agencies, organizations, and communities. The Council encouraged the NIDCR to stay informed about the issues involved, and efforts to resolve these issues, but to focus its efforts on specific areas where it could have maximal effect.

Panel Members. The Council emphasized that the panel should include representation from key minority groups and community-based organizations involved in education. Other potential panel members include individuals who have guided successful programs for revamping education, deans involved in curriculum development, successful science teachers in grades K-12, and bioengineers. Sources for identifying potential panel members include the Association of Academic Health Centers, which could help identify representatives from "integrated" centers, and Institute of Medicine reports on workforce issues.

Agenda Topics. The Council suggested a range of topics for the panel's discussions. These included: NIDCR participation in strengthening the pipeline of scientists, recruitment of students into dental research careers, innovative programs for research training, training issues for specific populations (e.g., minorities), and retention of trainees and investigators in research. Four topics related to strengthening the pipeline, which could be addressed by the panel are: ways to change the public's perception about research; opportunities for collaboration with the larger medical community on fostering science awareness in grades K-2; involvement of NIH scientists in promoting discussions of inquiry-based science education for K-12 teachers; and establishment of on-campus magnet "schools" at the NIH in collaboration with local elementary schools, high schools, and colleges.

The Council strongly encouraged the panel to solicit students' input on ways to attract individuals into research careers. Members suggested that NIDCR could conduct focus groups with individuals who are, and are not, interested in research; collaborate with professional organizations such as the American Association of Dental Schools to "harvest" comments from student members; and obtain input from others besides dental students (e.g., dental hygienists, potential Ph.D.s). The Council also suggested that the panel address mechanisms for recruiting and retaining foreign scientists in the United States (e.g., by creating partnerships with foreign universities).

The Council commented that few deans of U.S. dental schools have a research background and that research faculty are few. Three important issues in this regard, which relate to recruitment, are: enhancement of research in the dental curriculum, key roles and characteristics of mentors (perhaps defined through a series of case studies of successful mentors), and specification of the "research" required for specialty boards. An overriding issue, of course, is debt forgiveness, which continues to be a major problem in attracting dental students into research careers.

The Council emphasized that the focus of the panel and NIDCR should be on identifying gaps in the pipeline of dental researchers specifically and on creating innovative solutions to "plug" these gaps. Members encouraged the panel to begin with a "clean piece of paper" and to consider first the objectives of research (i.e., what work needs to be done). Innovative training approaches could then be designed based on these objectives. New models are needed, for example, to train investigators who could direct and conduct translational and/or clinical research. One possibility might be to encourage young investigators from universities to "rotate" into NIDCR's intramural laboratories within a defined program.

The Council encouraged the panel to not focus on degrees, but on the talents, interests, and skills needed to complete certain work. Members emphasized that training should be integrated across disciplines and that the NIDCR could partner with other NIH components and agencies (e.g., the National Science Foundation) to support multi-institutional programs. The panel also may wish to identify existing programs that are highly successful and to specify criteria for measuring the outcomes of NIDCR-supported training programs.

The Council emphasized that the recruitment and training of researchers from specific populations (e.g., minorities) should be given special attention. Some suggestions for enhancing minority involvement in research include active participation of NIDCR staff in annual meetings of minority organizations; regular publication of NIDCR articles in minority professional publications; distribution of NIDCR materials to minority organizations for distribution among members; organization of scientific symposia for minorities at annual meetings; and outreach to undergraduates and key minority undergraduate faculty at both minority and majority schools.

The Council noted that aggressive approaches (e.g., an increase in NIH stipends) are needed to retain NIDCR-trained investigators in research. Two major issues are: debt forgiveness, and the increased financial rewards offered by industry and dental practice.

In closing the discussion, Dr. Slavkin thanked the Council for its input and said that the NIDCR would follow up with Council members concerning individuals and organizations who could contribute to the panel's effort.

X. COMMENTS AND UPDATES

Craniofacial Morphogenesis Workshop

Dr. Ernesto Canalis commented on the workshop entitled "Toward a Molecular Understanding of Craniofacial Morphogenesis," which was held November 22-24, 1998, at the NIH. This 2-day meeting, organized by the NIDCR in collaboration with other NIH components and foundation support, attracted more than 350 scientists and included presentation of about 100 posters. Dr. Canalis said he was impressed by the number of participants attending and by the material that was presented, which mostly concerned molecular genetics. The two main topics were: the impact of genetic abnormalities on disease, and the role of specific genetic factors in craniofacial development.

Dr. Martha Somerman noted that the workshop was a highly engaging meeting of research leaders in the field and that she was pleased to be able to bring students to the workshop at no charge.

FY 2001 Budget-Planning Retreat

Dr. Caswell A. Evans, Jr., and Dr. Marjorie K. Jeffcoat commented on NIDCR's Winter Budget Planning Policy Retreat for FY 2001, which was held on December 16-17, 1998, in Airlie, Virginia. NIDCR staff meet three times a year in executive retreat to conceptualize science opportunities and

to plan activities and budgets. At the winter retreat, staff addressed major themes and objectives for FY 2001. A summary of the retreat was provided to the Council. Dr. Evans and Jeffcoat, who attended the retreat as Council representatives, noted that the session was very informative and productive, and they encouraged NIDCR to continue to invite Council members to the retreats. The Council asked that NIDCR give members advance notice of the dates for these meetings.

CLOSED PORTION OF THE MEETING

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 Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

XI. REVIEW OF APPLICATIONS

Grant Review

The Council considered 341 applications requesting \$62,025,696 in total costs. The Council recommended 232 applications for a total cost of \$41,335,118 (see Attachment II).

ADJOURNMENT

The meeting was adjourned at 2:00 p.m. on January 26, 1999.

CERTIFICATION

I hereby certify that the foregoing minutes are accurate and complete.

Dr. Harold C. Slavkin
Chairperson
National Advisory Dental and
Craniofacial Research Council

Dr. Dushanka V. Kleinman
Executive Secretary
National Advisory Dental and
and Craniofacial Research Council

ATTACHMENTS

- I. Roster of Council Members
- II. Table of Council Actions
- III. Director's Report to the NADCRC, January 1999

NOTE: A complete set of open-portion handouts are available
from the Executive Secretary.