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 22, 2001
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 22, 2001

The 163rd meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on January 22, 2001, at 8:35 a.m., in Building 45, Conference Room E1&2, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:35 a.m. to 12:50 p.m., followed by the closed session for consideration of grant applications from 1:45 p.m. until adjournment at 5:00 p.m. Dr. Lawrence A. Tabak presided as Chair.

Members Present:

Dr. John F. Alderete
Dr. Marilyn Carlson
Dr. D. Walter Cohen
Dr. Samuel F. Dworkin
Dr. Raymond J. Fonseca
Dr. Jay Alan Gershen
Dr. Howard K. Kuramitsu
Dr. Harold Morris
Dr. Linda C. Niessen
Dr. Leslie A. Raulin
Dr. Joan Y. Reede
Dr. Martha J. Somerman
Ms. Kim S. Uhrich
Dr. Everett Vokes

Members of the Public Present:

Dr. Richard Carr, American Dental Education Association (ADEA), Washington, D.C.
Dr. Aida A. Chohayeb, Professor, Howard University, Washington, D.C.
Dr. Robert Collins, Deputy Executive Director, American Association for Dental Research (AADR), Alexandria, VA
Dr. Karl Haden, Division of Educational Policy and Research, ADEA, Washington, D.C.
Dr. Frank Macrina, Edward Meyers Professor and Director, Virginia Commonwealth University (VCU) Philips Institute, Richmond, VA, and Chair, Board of Scientific Counselors, NIDCR

Dr. David Relman, Assistant Professor of Medicine, Microbiology, and Immunology, Stanford University, Palo Alto, CA
Dr. Marsha Rerehman, Contractor, ROW Sciences, Rockville, MD
Dr. John D. Rugh, Professor, University of Texas Health Sciences Center at San Antonio
Dr. Ruth M. Ruprecht, Professor of Medicine, Harvard Medical School and the Dana-Farber Cancer Institute, Boston, MA
Dr. Eli Schwarz, Executive Director, AADR and International Association for Dental Research, Alexandria, VA

Federal Employees Present:

National Institute of Dental and Craniofacial Research:

Dr. Margo Adesanya, Senior Scientist, Craniofacial Epidemiology and Genetics Branch, Office of Science Policy and Analysis (OSPA)
Ms. Carolyn Baum, Committee Management Specialist and Council Secretary, OSPA
Dr. Henning Birkedal-Hansen, Scientific Director, NIDCR, and Director, Division of Intramural Research (DIR)
Dr. Norman S. Braveman, Associate Director, Office of Clinical, Behavioral, and Health Promotion Research, Division of Extramural Research (DER)
Dr. Patricia S. Bryant, Health Scientist Administrator, Behavioral and Health Promotion Research, DER
Ms. Sharrell S. Butler, Diversity Program Manager, Office of the Director (OD)
Ms. Maria Teresa Canto, Public Health Research Specialist, OSPA
Ms. Jennifer Connell, Grants Technical Assistant (GTA), DER
Mr. George J. Coy, Chief, Financial Management Branch, Office of Administrative Management (OAM)
Ms. Mary Daum, Writer, Public Information and Liaison Branch (PILB), Office of Communications and Health Education (OCHE)
Ms. Jody Dove, Public Information Specialist, PILB, OCHE
Dr. Thomas Drury, Health Statistician, Health Promotion and Disease Analysis Branch (HPDAB), OSPA
Ms. Yvonne H. du Buy, Associate Director for Management, and Director, OAM
Dr. Caswell A. Evans, Project Director and Executive Director, Report on Oral Health, OSPA
Ms. Harriett Ganson, Planning and Evaluation Officer, OSPA
Dr. Isabel Garcia, Special Assistant for Science Transfer, OCHE
Ms. Christen Gibbons, Computer Specialist, Information Technology and Analysis Branch, OCHE
Dr. Sarah L. Glavin, Evaluation Officer, OSPA
Dr. Kenneth A. Gruber, Chief, Chronic Diseases Branch, DER
Ms. Denise Halley, GTA, DER
Dr. Kevin Hardwick, International Health Officer, Office of International Health

Dr. H. George Hausch, Chief, Scientific Review Branch (SRB), DER
Ms. Deane K. Hill, Computer Programmer, Planning, Evaluation, and Legislation Branch, OSPA
Ms. Alice Horowitz, Health Promotion Officer, OSPA
Ms. Lorrayne Jackson, Diversity Programs Specialist, and Co-Director, Diversity Programs, DER
Dr. Bernard W. Janicki, Special Assistant for Planning, Technology Transfer, and Management, DER
Mr. William M. Johnston, Consultant, Biomaterials, Biomimetics, and Tissue Engineering Branch, DER
Ms. Erika Joyner, GTA, DER
Ms. Mary Kelly, Program Assistant, PILB, OCHE
Ms. Sandra King, Secretary, Diversity Program, OD
Dr. Dushanka V. Kleinman, Deputy Director, NIDCR, and Executive Secretary, NADCRC
Dr. Eleni Kousvelari, Chief, Biomaterials, Biomimetics, and Tissue Engineering Branch, DER
Ms. Wendy A. Liffers, Director, OSPA
Dr. James A. Lipton, Assistant Director, Office of Training and Career Development, DER
Dr. Yujing Liu, Scientific Review Administrator, DER
Dr. Jack London, Special Assistant to the Director, DIR
Dr. Dennis F. Mangan, Chief, Infectious Diseases and Immunity Branch, DER
Dr. J. Ricardo Martinez, Director, DER
Ms. Angela Miez, GTA, DER
Dr. Ruth Nowjack-Raymer, Public Health Research Specialist, OSPA
Mr. Robert Palmer, Senior Research Assistant, DIR
Dr. Maryann Redford, Health Scientist Administrator, Office of Clinical, Behavioral, and Health Promotion Research, DER
Dr. Martin Rubinstein, Chief, Grants Management Branch, DER
Dr. Denise Russo, Program Administrator, AIDS Program, Infectious Diseases and Immunity Branch, DER
Dr. Ann L. Sandberg, Chief, Neoplastic Diseases Branch, and Director, Comprehensive Centers of Discovery Program, DER
Dr. Robert O. Selwitz, Senior Dental Epidemiologist, Health Promotion Branch, OSPA
Dr. Jonathan Shenkin, Dental Public Health Resident, OSPA
Ms. Patricia Sheridan, Writer, OCHE
Dr. Yasaman Shirazi, Scientific Review Administrator, DER
Dr. Rochelle Small, Chief, Craniofacial Anomalies and Injuries Branch, DER
Ms. Cheryl Stevens, Special Assistant for Operations, OD
Dr. Sharon M. Wahl, Chief, Oral Infection and Immunity Branch, DIR
Ms. Tracy Walker, Secretary, OSPA
Dr. Philip Washko, Scientific Review Administrator, DER
Ms. Dolores A. Wells, Program Analyst, OD
Ms. Mary Ann Williamson, Computer Specialist, Office of Information Technology, OD
Dr. Guo Zhang, Health Scientist Administrator, DER

Other Federal Employees:

Dr. C. R. Buchanan, Deputy Director for Dentistry, Department of Veterans Affairs, Washington, D.C.
Dr. Bruce Dye, National Center for Health Statistics, Centers for Disease Control and Prevention
Dr. Fred Eichmiller, Director, Paffenbarger Research Center of the ADA Health Foundation, National Institute of Science and Technology, Department of Commerce, Gaithersburg, MD
Cpt. Gary Kaplovitz, Dental Officer, U.S. Coast Guard
Dr. Robert Mecklenburg, Consultant, National Cancer Institute, NIH

OPEN PORTION OF THE MEETING

I. CALL TO ORDER

Dr. Lawrence Tabak called the meeting to order. He welcomed all attendees and asked them to introduce themselves. Dr. Tabak introduced and welcomed three new members of the Council: Drs. Ray Fonseca, Howard Kuramitsu, and Linda Niessen. The agenda for the meeting focused on NIDCR's research portfolio in infectious diseases and immunity.

II. REPORT OF THE DIRECTOR

Dr. Tabak highlighted several items from the written Report of the Director (see Attachment III). He noted first that the Institute is deeply saddened by the recent deaths of two staff members: Ms. Kimberly Webb, statistical assistant, Craniofacial Epidemiology and Genetics Branch, Division of Intramural Research (DIR), and Dr. David Barmes, special expert for international health, Office of International Health.

Reporting on the budget, Dr. Tabak said that NIDCR has received a budget of approximately $306.2 million for fiscal year (FY) 2001. This budget, which represents a 13.8 percent increase over FY 2000, will allow the Institute to restore some funding cuts on extramural awards. Because of continuing obligations, the Institute will continue to determine levels of support on a grant-by-grant basis, as guided by priorities assigned during peer review. For first-time investigators, newly supported by the NIDCR, the Institute is committed to maintaining the budgets recommended by the study sections.

With the concurrence of the Council, the NIDCR is changing the funding level and eligibility requirements for the R03 program to provide awards up to $100,000 over a 2-year period and to limit eligibility to new investigators. To enhance future program flexibility, the NIDCR will impose a

moratorium on P01 applications. All noncompeting commitments to current grantees will continue, as indicated in their notice of award, but no unsolicited applications for new (type 1) P01s will be accepted after February 1, 2001; no renewal applications (type 2) for P01s ending by September 30, 2002, will not be reviewed. Because of the uncertainty of future budgets, Dr. Tabak encouraged individual investigators participating in a P01 award to submit R01 applications for support in case their competing continuations are not funded. He emphasized that NIDCR staff will work closely with the extramural community to facilitate use of mechanisms supporting interdisciplinary research and to help identify mechanisms supporting unique national core resources.

Dr. Tabak noted that the Institute is committed to researching problems unique to NIDCR (e.g., caries, periodontal diseases, oral and pharyngeal cancers, chronic disabling diseases, complex oral health problems of special-needs patients). In addition, the Institute is proceeding with efforts related to health disparities and is committed to supporting science and research training in this area at the highest level. A revised NIDCR strategic plan for reducing health disparities will be available soon on the NIDCR home page, and the Institute has established an NIDCR committee to oversee all Institute activities in this area.

In closing, Dr. Tabak noted that the NIH is establishing a National Institute of Biomedical Imaging and Bioengineering, based on legislation provided by Congress. Dr. Tabak serves on the task force that is developing the scope of this new institute.

Discussion

Dr. Jay Gershen, Executive Vice Chancellor, University of Colorado Health Science Center, Boulder, noted that the University of Colorado recently received $250 million, the largest gift ever given to a public university, for research on cognitive disabilities. The gift, from Claudia and Bill Coleman, who is the founder of Sun Microsystems, will be used to support interdisciplinary research on the entire range of cognitive disabilities. Dr. Gershen noted that the university looks forward to leveraging these funds with the NIH, including the NIDCR.

III. APPROVAL OF MINUTES

The minutes of the Council's meeting on September 21-22, 2000, were considered and unanimously approved.

IV. FUTURE COUNCIL MEETING DATES

The following dates for future Council meetings were confirmed:

June 12-13, 2001
September 24-25, 2001

January 28-29, 2002
June 10-11, 2002
September 26-27, 2002

V. OVERVIEW OF NIDCR'S INFECTIOUS DISEASES AND IMMUNITY RESEARCH PORTFOLIO

Dr. J. Ricardo Martinez, Director, Division of Extramural Research (DER), NIDCR, presented a brief overview of infectious diseases and immunity programs within NIDCR. He noted that oral infectious diseases continue to be a major public health problem in the United States and that research on oral biology, including immunology and immunity, is an important component of NIDCR's extramural and intramural portfolio. In FY 2000, infectious diseases and immunity was the largest component of the extramural portfolio, accounting for approximately $45.6 million, which supported 169 awards, or about 31 percent of all extramural research project grants (RPGs).

Division of Extramural Research

Dr. Dennis F. Mangan, Chief, Infectious Diseases and Immunity Branch, DER, described the goals, programs, awards, and categories of research supported by DER in infectious diseases and immunity. The branch's goals and responsibilities are to identify the best areas of science and the researchers and to provide the necessary resources for the research and the oversight on the use of these resources. The portfolio can be categorized into five areas: microbial ecology, AIDS, immunology, systemic diseases, and microbial genomics. Each area encompasses several research directions. Research on diagnosis, prevention, and treatment of oral infectious diseases is common to all areas, and the science in each area overlaps and is relevant to other areas.

Elaborating on NIDCR's support of research in microbial genomics, Dr. Mangan noted two major initiatives. NIDCR-supported extramural researchers are completing the sequencing of genes for principal bacterial pathogens in the oral cavity (*Porphyromonas gingivalis*, *Treponema denticola*, *Streptococcus mutans*, *Actinobacillus actinomycetemcomitans*, *S. sanguis*, and *Candida albicans*), which will be achieved in 2001-03. In addition, by 2002, researchers will have incomplete sequences of the genes for six other organisms, which will also be made available to the public.

In FY 2000, the branch supported a total of 239 awards (including RPGs), at a cost of approximately $53 million. Approximately two-thirds of this support (~140 awards, $36 million) was for noncompeting awards, and approximately one-third (~90 awards, $17 million) was for new and competing awards in FY 2000. Awards in the microbial ecology, AIDS, and immunology areas comprised the bulk of the branch's activity in FY 2000. The major disease categories were periodontitis (which received about $34 million in funding), AIDS (~$17.5 million), caries (~$17.2 million), and biofilm (plaque) (~$12.2 million).

Approximately 15 different mechanisms of support were utilized to support the research. Most awards (59 percent) were investigator-initiated (R01) RPGs. Other mechanisms supported small grants, meetings, developmental research, new investigators, cooperative agreements, program projects, two Comprehensive Centers of Research, small business awards, training of international scientists, contracts, and an interagency agreement with the Department of Energy to develop a web-based, user-friendly microbial genome database. Approximately 3.2 percent of the branch's funds supported 32 international awards, to foreign scientists, U.S. scientists or institutions engaged in international collaborations.

In addition to the branch's program, other DER branches support research relevant to infectious diseases and immunity. In FY 2000, these branches made 24 awards for behavioral and clinical research, tissue engineering, and studies of chronic or neoplastic diseases. The NIDCR also collaborates extensively across the NIH. In FY 2000, the NIDCR was designated the primary or secondary institute for 35 awards, costing approximately $2.35 million.

In closing, Dr. Mangan highlighted opportunities for future research on infectious diseases and immunity: microbial ecology (especially biofilms), AIDS (oral transmission), immunity (mucosal vaccines, innate recognition), systemic disease (clinical intervention, oral-systemic effects), and genomics (functional genomics).

Division of Intramural Research

Dr. Henning Birkedal-Hansen, Scientific Director, NIDCR, and Director, DIR, shared some thoughts and philosophies about the intramural program in infectious diseases and immunity. He noted three major reasons for the Institute's interest in this research area: caries and periodontal disease, which were the basis for establishing the Institute in 1948, and AIDS, beginning about 1981. The relevant research disciplines include microbiology, mucosal immunity, and mineral chemistry and metabolism, which has yielded the most progress and benefit during the past 50 years through research on dental fluorosis and the caries-protective effect of fluorides.

Dr. Birkedal-Hansen noted that the current understanding of caries and periodontal disease is based on a 40-year-old paradigm to which bits of information have been added over the years. Contrary to most other diseases, dental caries and periodontal disease can be treated and prevented even though many of the details of the diseases are not understood. It is known that caries involves the interaction of

microorganisms, diet, and host factors and is transmissible in animals. Caries may be caused in experimental animals by several different microorganisms, is likely caused in humans by lactobacilli and streptococci, and can be prevented by applying fluoride and/or removing the biofilm. With respect to periodontal disease, it is known that the course of gingivitis and periodontitis can be modified by removing the biofilm. The disease course for both caries and periodontal disease varies widely among individuals, which suggests that the host's response strongly influences the development of these diseases. Much progress has been made, and researchers are now seeking additional information to validate, or overthrow, the existing paradigms.

With respect to the microbiology of other infectious diseases, intramural researchers are focusing on virology studies of AIDS and herpes simplex and are studying streptococcal genetics and metabolism and anaerobic microbiology. In humoral, cellular, and mucosal immunity researchers are focusing on vaccines, inflammatory cell responses, and cytokines and growth factors. Fluoride continues to be the focus of studies of mineral chemistry and metabolism.

Dr. Birkedal-Hansen noted the intramural leaders who have advanced the understanding of infectious diseases and immunity over the years. Currently, Dr. Sharon Wahl directs DIR's Oral Infection and Immunity Program, which consists of eight independent investigators with their own research groups. Dr. Birkedal-Hansen briefly described the program's five research areas in FY 2001: mucosal immunity, microbial toxins, streptococcal carbohydrate metabolism, biofilm, and virology. He highlighted two broad areas of particular promise for the future: biofilm and microbial-host interactions. In closing, he noted that one never knows where the next discovery will come from and that research for dental caries and periodontal diseases may shift the long-standing paradigms.

Discussion

In response to questions from the Council, Dr. Birkedal-Hansen noted that the NIDCR has one mission, which underpins both the DER and DIR programs, and that the two programs utilize different funding mechanisms to accomplish this mission. The goals of reducing and eliminating dental caries and periodontal disease are the same as in 1948. To achieve these goals, broad thinking and research on basic underlying processes are essential. Dr. Birkedal-Hansen emphasized that solutions to local problems are often global. In the quest for answers, intramural researchers collaborate extensively with colleagues in other NIH institutes and centers (ICs) and the extramural community. These collaborations are described in a booklet which DIR prepares and distributes each year.

VI. AN UPDATE ON MECHANISMS OF AIDS TRANSMISSION

Dr. Ruth M. Ruprecht, Professor of Medicine, Harvard Medical School, Boston, Massachusetts, and a current NIDCR grantee, presented an overview of research on mechanisms of oral AIDS virus transmission. She focused on two topics: host issues, and virus issues. Regarding host issues, the three

key research questions have been: (1) At what age does oral transmission of HIV/AIDS occur, and are neonates, infants, and adults equally susceptible to HIV infection after oral exposure to the virus? (2) What is(are) the site(s) of viral entry after oral inoculation, and what is the role of mucosal lesions in the oral cavity or the upper gastrointestinal tract mucosa? And, (3) how does the virus cross intact mucosa?

Dr. Ruprecht summarized current research to answer these questions, describing studies of the simian immunodeficiency virus (SIV), the human HIV pathogen, and a chimeric virus (SHIV) combining SIV and HIV which can be grown and replicated in monkey cells. She reported data from nonhuman primate studies and from human studies, including research in her laboratory which led to development of a successful primate model (rhesus monkeys) for studying prevention of oral virus transmission and for testing vaccines and antibodies against HIV infections.

Dr. Ruprecht noted that monkeys of all ages are susceptible to SIV and/or SHIV infection by the oral route and that oral transmission of these viruses has been documented in a number of studies conducted in the United States and Europe. Further, in the absence of mucosal lesions, the oral mucosa is easier for the virus to traverse than the rectal mucosa.

In humans, the situation is more difficult to dissect. Studies clearly show that HIV can be transmitted orally from mothers to infants by breastfeeding. Intrapartum HIV transmission may also involve the oral route, and epidemiological evidence and case reports implicate the oral route of HIV transmission for adults (i.e., through unprotected oral sex). Epidemiological or experimental evidence implicates two sites of viral entry after oral exposure: the oral mucosa and the tonsils. Saliva is known to contain substances that inhibit HIV; however, although there is little or no evidence for oral transmission of HIV from the saliva of an infected person, the inhibitory substances in the saliva are not sufficient to protect uninfected individuals from entry of the virus after oral exposure.

Regarding virus issues in oral transmission, Dr. Ruprecht noted four key research questions:
(1) Does oral exposure to HIV-infected cells, rather than cell-free virus, result in systemic infection?
(2) Are virus strains with certain co-receptor use (tropism) (i.e., a predilection to replicate in either macrophages or T cells) more infectious after oral exposure than others? (3) How infectious is the oral route compared to other mucosal or intravenous routes for different virus strains? And, (4) does the mucosa in the upper gastrointestinal tract act as a bottleneck to permit preferential passage of certain quasi-species when uncloned virus is inoculated? Dr. Ruprecht reported that initial studies in nonhuman primates suggest that cell-free virus is the most important mode of infection orally and that certain virus strains might be more infectious than others after oral exposure.

VII. MICROBIAL BIODIVERSITY

Dr. David Relman, Assistant Professor of Microbiology and Immunology and of Medicine, Stanford University, Palo Alto, California, and an NIDCR grantee, spoke on microbial diversity and oral health. He

noted that this broad area of research offers many more questions than answers and is an exciting field of study with significant unrealized potential that is attracting a wide variety of investigators. He presented an overview of microbial diversity in general and then commented specifically on oral ecology, health, and disease and important areas for further research.

Dr. Relman emphasized that a significant number of human-associated microbes, some of which may be important causes of both disease and health, remain uncharacterized. Over the past 2+ billion years, three separate lineages of cellular life have emerged in the "tree of life" (rRNA sequences): bacteria, archaea, and eucarya. The bacterial world alone includes at least 40 divisions of life, each of which is as diverse as the entire animal kingdom. Only seven of the divisions are known to contain pathogens, and four of these account for approximately 90 percent of all known cultivated organisms. The vast majority of the bacterial world has not been cultivated. Further, the world of archaea, the largest and most diverse group of cellular life on earth, is virtually unexplored regarding its potential to cause disease.

Yet, the benefits to the host of the human commensal flora are enormous. Among the benefits already attributed to these flora are vitamin production, food degradation, resistance to colonization by outside organisms, and maturation and function of the gastrointestinal tract and immune system.

New methods and technologies now make it possible to study these functions and actions in greater detail. Dr. Relman noted that application of the DNA polymerase chain reaction (PCR) technique has revolutionized understanding of microbial diversity. Using this technique, scientists can obtain and grow DNA sequences directly, to analyze and infer the phylogeny of putative organisms and then to design specific probes for certain bacteria. Clinical comparison with conventional methods of cultivation showed that the PCR approach detected approximately 90 percent of the previously unrecognized bacteria (versus about 17 percent) in a sample from an individual with mild gingivitis. Use of quantitative hybridization methods further allows researchers to quantify different bacterial groups within human flora and to assess variability, which can be substantial, over time and among different hosts. More efficient quantification methods, such as a high-density hybridization format (microarray), are needed to tailor and conduct intensive surveys of clinical samples.

Dr. Relman noted several ongoing studies using these techniques to probe uncultivated divisions of bacteria that may be important in the oral cavity. Thus, the diversity of known, and potentially clinically relevant, microbes is expanding. Dr. Relman suggested, from an ecological perspective, that a complexity of genes and microbes may be involved in specific clinical problems (e.g., gingivitis, glossitis, aphthous ulcers) associated with a disrupted ecosystem of oral microbes. In addition, PCR studies suggest bacterial DNA may be found in the bloodstream of healthy people. Dr. Relman noted that a growing group of investigators in ecology are intrigued by the evenness and richness of diversity between different individuals at different sites over time and by the effects of perturbations on the human ecosystem.

Some of the interesting questions are: What is the structure of an optimal human endogenous microbial ecosystem and does this promote and maintain human health? Is there decreased diversity in settings of

disease such as periodontitis? Does the mouth conform to the "intermediate disturbance hypothesis" (i.e., low microbial diversity at low and high levels of physical disturbance, and maximal diversity at intermediate levels of disturbance)? Do organisms adapted for different sites (e.g., in the mouth) compete with each other? Can successful strategies for maintaining oral health be predicted based on simple ecological principles?

Other aspects of the microbial ecology of the commensal flora relevant to oral health and disease include spatial arrangements and physiological activity of the flora and the host response. For example, what are the physiological properties of specific organisms and do they contribute to maintaining the oral ecosystem? Researchers are using techniques such as PCR, in situ fluorescence hybridization, and autoradiography to explore such questions. Also, with genetic and informatics techniques and the availability of the human genome sequence, researchers can develop detailed expression profiles to understand and predict a host's response to specific flora. The advantages for clinical prediction (e.g., of periodontitis) are significant.

Dr. Relman concluded that strategies and approaches are now available which, in combination with an interdisciplinary perspective, could revolutionize understanding of the function, activity, and interaction of microbes with themselves and with the host. This knowledge could ultimately lead to new approaches to treating and preventing disease.

VIII. MUCOSAL SUSCEPTIBILITY AND RESISTANCE TO HIV

Dr. Sharon M. Wahl, Chief, Oral Infection and Immunity Branch, DIR, NIDCR, addressed one research area in the branch's program, mucosal immunity and HIV/AIDS. Focusing specifically on mechanisms of resistance, Dr. Wahl noted that 90 percent of all infections begin at the mucosal membrane and that mucosal immunity is not a trivial concern because the mucosal immune system is the largest immune system in the body. She also noted that none of the mechanisms of resistance are impermeable. HIV is no exception. Most HIV infections occur at the mucosal membrane and, each day, an estimated 16,000 individuals are newly infected worldwide. The rates of infection by mucosal contact continue to increase for women, and particularly, minority women. Research on the mechanisms of infection and resistance to infection is essential.

Dr. Wahl summarized four areas of NIDCR research: mucosal susceptibility, maternal-infant transmission, transmission through breastfeeding, and HIV activity in the tonsils. To address potential differences in mucosal susceptibility to HIV, the NIDCR is collaborating in the Women's Interagency HIV Study. NIDCR researchers have undertaken three studies in sequence, to compare HIV-1 RNA in the blood with two mucosal compartments (the genital tract and the oral cavity), examine parameters (antiretroviral therapy, presence of co-pathogens, host defense) affecting differential expression of HIV in the three compartments (blood, genital tract, oral cavity), and determine the correspondence of infectious HIV in the compartments. The studies of blood and mucosal samples taken from HIV-positive women show that

HIV-1 RNA levels, the effect of the parameters, and the presence of infectious HIV were distinctly different among the three compartments.

Dr. Wahl noted that the findings indicate that the mucosal compartments represent a unique microenvironment. In contrast to blood, the mucosal compartments show HIV RNA, but minimal detection of infectious HIV; a potentially profound influence of co-pathogens (e.g., *Candida albicans*, cytomegalovirus, Epstein-Barr Virus, papilloma virus, trichomonas); distinct levels of innate host defense molecules (secretory leukocyte protease inhibitor, or SLPI, and thrombospondin); and a specific local immune response. In addition, in some cases, the mucosal sites may be potential viral reservoirs protected from therapy. She noted that additional analysis of these potential reservoirs is needed to define other parameters that may affect the infectious nature of HIV.

Studies of maternal-infant transmission are being conducted in collaboration with extramural researchers in the United States and South Africa. Dr. Wahl noted that vertical transmission of HIV is a serious world health problem. The World Health Organization estimates that 1.5 million children are currently infected with HIV and that this number may increase tenfold in the next decade. Under some circumstances, up to 50 percent of children born to HIV-infected mothers become infected with HIV. In a small study comparing pregnant women who were HIV-sero-negative and HIV-positive and their infants after birth, analyses showed that SLPI levels were significantly lower in the vaginal mucosa of mothers who transmitted HIV to their infants. Dr. Wahl noted that this clue to the importance of innate factors needs to be confirmed in larger studies.

In a collaborative study of HIV transmission through breastfeeding, conducted in Burkina Faso, NIDCR researchers are comparing postnatal levels of potential antiviral molecules (SLPI and thrombospondin) in samples of saliva and mature breast milk from HIV-negative and HIV-positive women who did and did not transmit HIV to their infants. The results thus far show that SLPI levels are very low and do not approach threshold levels for antiviral activity in mature breast milk samples regardless of the women's HIV or transmission status, whereas SLPI levels are high enough in the saliva to inhibit HIV; the converse results were found for thrombospondin. Interestingly, colostrum showed very high SLPI levels, comparable or higher than in saliva, although breast milk showed no significant SLPI after a few weeks. High levels of other antiviral molecules (thrombospondin, HIV antibodies, chemokines) were also found in colostrum, indicating that there may be a transient period of neonatal protection against HIV. Dr. Wahl suggested that researchers may be able to define a window of time when breastfeeding affords less risk of transmission and may eventually be able to enhance or extend the expression of inhibitors to continue protection.

She noted further that these findings, and those reported earlier by Dr. Ruprecht (see section VI above), demonstrate that the mucosa may be both a primary and a secondary site of HIV infection. Tonsils, with their fascinating mucosal architecture, share this capability. NIDCR researchers created an in vitro model to study the susceptibility of tonsil cells, from HIV sero-negative individuals, to HIV. The in vitro studies show that the cells are highly sensitive to HIV, much more so than are cells from peripheral blood. The

researchers are continuing the studies to identify susceptibility factors (e.g., interleukins, transforming growth factor-beta, interferon) in tonsil cells, to help define potential mechanisms for intervention.

In closing, Dr. Wahl noted that the ultimate goal of all this research is to prevent transmission of HIV and to identify opportunities for intervention, including behavioral modification, and education. Toward this goal, the NIDCR will continue to explore potential innate and adaptive immune factors that affect transmission.

IX. NIH NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES

Dr. John Ruffin, Director, National Center for Minority Health and Health Disparities (NCMHHD), NIH, described the role and future activities of this new NIH center, which was established on November 22, 2000, in accordance with The Minority Health and Health Disparities Research and Education Act of 2000. The center replaces the previous NIH Office of Research on Minority Health (ORMH), which was also headed by Dr. Ruffin.

The legislation identifies three purposes for the NCMHHD: "...to conduct and support research and training, disseminate research-based health information, and develop other programs with respect to minority health conditions and other populations with health disparities." The legislation also stipulates that the center director has responsibility for coordinating all research conducted or supported by the NIH on minority health disparities and other health disparities and that the director will chair a trans-NIH task force to develop a comprehensive plan and budget within the next 12 months for all NIH-supported research on minority and other health priorities. Dr. Ruffin noted that the existing NIH strategic plan in this area will serve as the foundation for this effort and that the public comment period on this plan has been extended.

The legislation further stipulates that the center will promote coordination and collaboration among the ICs and will provide funds for the awarding of peer-reviewed grants for innovative projects that address high-priority areas of minority health research. Dr. Ruffin noted that the center, in contrast to the ORMH, will have grant-making authority, but will continue to view itself as an extension of the other ICs and seek partnerships with these components. The legislation also provides for an advisory council to advise the center director, identification and support of centers of excellence in research and training, establishment of a research endowment program to support the centers, and initiation of a new extramural loan repayment program.

The legislation includes stringent evaluation and reporting requirements. For the Congress, the center must prepare an annual report of activities; a 5-year evaluation of the center's effect on disparity research, planning, and coordination at the NIH; and a report that recommends methodologies for determining the extent of NIH's resources dedicated to minority health and health disparities.

The center also will work closely with other agencies (e.g., Agency for Health Care Research and Quality, Health Resources and Services Administration) and the National Academy of Sciences on studies and efforts related to health disparity populations. These populations are defined in the legislation as populations with "...a significant disparity in the overall rate of disease incidence, prevalence, morbidity, mortality, or survival rates...as compared to the health status of the general population." Dr. Ruffin noted that health disparities exist among populations of all races and ethnicities and that, in contrast to the ORMH, the new center will focus on all medically underserved populations. Health disparities research is defined in the legislation as "basic, clinical, and behavioral research on health disparity populations, including individual members and communities of such populations that relates to health disparities, including the causes of such disparities and methods to prevent, diagnose, and treat such disparities."

Dr. Ruffin emphasized that existing financial commitments and ongoing initiatives previously established between the ORMH and other NIH components will continue and that IC programs will not be transferred to the new center. In coordination with the ICs, the center is reviewing all programs to determine the best administrative site for them and possible expansion of support. The center also will continue its broad consultative process, involving ICs and the extramural research and education communities, to develop research priorities. Overall priorities will remain the same as in the ORMH: inclusion of minorities in biomedical research, collaborative research programs between majority and minority institutions, expansion of research training opportunities for health care professionals, increased utilization of NIH minority research supplements, increased competitiveness of minority research, and development of a coordinated research and training information system.

In closing, Dr. Ruffin noted that the evolution from an office to a center has not changed the core mission, but has provided more tools for fulfilling this mission. The center will continue to place a very high value on its partnerships with the NIDCR and other ICs and does not anticipate significant changes in this interaction. For FY 2001, the NCMHHD has a budget of approximately $130 million, which includes approximately $96 million already committed by the ORMH, leaving about $40 million to fund the new activities authorized by Congress. Dr. Ruffin commented that the challenge in the next 2 years will be to set priorities and to match the center's expanded authorities with its appropriation.

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.

X. REVIEW OF APPLICATIONS

Grant Review

The Council considered 467 applications requesting $135,166,070 in total costs. The Council recommended 339 applications for a total cost of $83,937,241 (see Attachment II).

ADJOURNMENT

The meeting was adjourned at 5:00 p.m. on January 22, 2001.

CERTIFICATION

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

_____	_____
Dr. Lawrence A. Tabak	Dr. Dushanka V. Kleinman
Chairperson	Executive Secretary
National Advisory Dental and Craniofacial Research Council	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 2001

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