ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF DENTAL RESEARCH

FISCAL YEAR 1972

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

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U. S. NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

July 1, 1971 - June 30, 1972

Compiled by

Office of Program Studies and Analysis

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

Preface

This issue of the NIDR Annual Report - FY'72, reflects a novel departure in format, which we believe conveys more concisely and yet more meaningfully the total activities of the past year. Morover, it is organized in a manner which is calculated to increase its usefulness both to the community of science, whose primary concern is the substance of research, as well as to the various echelons of management, to whom information regarding the effective marshalling of fiscal and manpower resources is of prime interest.

Functionally, the principle alterations in presentation derive from:

----expansion of the Notice of Research Project (PHS-166), normally completed at this time of the year for the Science Information Exchange, so as to include those items of management import previously presented as an integral part of the individual narrative project report. This alteration in the SIE report format was made feasible by operational changes undertaken by SIE in the way in which they store and retrieve information.

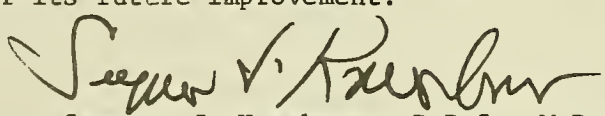
----synthesis of intramural narrative progress reports into a format of presentation on a sectional rather than an individual basis, so as to state more clearly the scientific purposes, progress and research directions of these fundamental organizational units of the Institute.

----identifying more distinctly those segments of the Institute's research undertaken through collaborative contract support, particularly in our recently expanded National Caries Program. As in the case of individual intramural research projects, the conventional SIE format (PHS-1688) was adapted to this purpose.

----addition of a variety of indexes to assist the user in answering almost any question which might arise about intramural or contract research projects in force during the fiscal year.

----color coding of various sections of the overall report so as to make it more convenient to use.

We acknowledge that because of the innovative nature of this effort, there may be a number of errors or oversights which will require corrections in future years. In general, however, we are pleased with this initial effort, and invite your suggestions for its future improvement.



Seymour J. Kreshover, D.D.S., M.D.
Director
National Institute of Dental Research

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REPORT OF THE DIRECTOR

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1971 - June 30, 1972

by

Seymour J. Kreshover

Pursuant to the request made by the Senate Committee on Appropriations in its report on FY 1972 appropriations, an evaluation of the Institute's five-year plan for the optimum development of the Nation's dental research effort was made and forwarded to the Committee. The evaluation related to the criteria articulated in the general statement of the Committee's report, i.e., directing the Institute's resources at "those disease problems that are most important and widespread, where effective means for dealing with the problem are available, where new opportunities have emerged, and where the likely benefits justify the expected costs."

The Institute initiated a series of meetings preparatory to the launching of an intensive program on periodontal disease as directed and authorized by the Congress in the passage of the FY 1972 appropriations act. Participants in these meetings included internationally recognized leaders in periodontal disease research. As a result, action was taken to intensify extramural and direct research on the pervasive and complex problem of periodontal disease which affects an estimated 75 million Americans.

When the Institute mounted the National Caries Program as a special research and development initiative, a new position of Special Assistant to the Director was established to provide a focal point of leadership and co-ordination. As the Program evolved and matured, it became evident that a more structured and self-contained organization was required for optimum management and evaluation. Accordingly, the position of Associate Director for the National Caries Program was set up with delegated authority and responsibility for the planning and direction of the Institute's total efforts in this area. Concurrently, staff concerned with extramural grants, research contracts, and intramural investigations were transferred to the new organizational component.

As the total NIH community of categorical Institutes became more involved with the planning and administration of research contracts as the principal means of conducting targeted research and development programs, the Dental Institute participated in a study as to the possible delegation of authority to award such contracts. The criteria emanating from the study permitted the Institute to have such a delegation of authority as a necessary means

of expediting the progress of the National Caries Program. The new authority was vested in the Chief, Office of Collaborative Research, and steps were taken to strengthen and expand the staff of that office in order to assure proper implementation. A somewhat related action was the establishment of a Contract Review Committee to examine proposed contracts and recommend approval or disapproval thereof to the Director, NIDR.

The Institute has had a long-standing arrangement with the National Bureau of Standards whereby support was provided to a small dental research section concerned primarily with the application of the physical sciences to problems of dentistry. In order to obtain a closer coordination with the Institute's direct research operations, the Director of Intramural Research was designated as the liaison and project officer on NBS dental research studies supported by NIDR and the latter activities were viewed as collaborative extensions of the Institute's intramural investigations.

The National Institute of Dental Research, in common with the rest of the NIH and DHEW community, was required to operate under a set of restrictions governing the number of employees and the average grade of the civil service employees under the General Schedule pay system. These restrictions have impeded the Institute's ability to employ new investigators and supporting staff as program needs dictate and have necessitated additional records in order to maintain control and prepare reports.

During the reporting period, the NIDR EEO Committee was expanded to fourteen members for better organizational coverage, a regular monthly meeting time established, and a new chairman and recording secretary appointed.

Activity directed toward increasing the number of women professionals has resulted in seven appointments and three promotions of women to positions GS-11 or above, six of which require a doctoral degree. A seventh female Ph.D. is scheduled to enter on duty in July 1972.

Efforts to appoint minority members to advisory committees have met with some success with the January 1, 1972 NIDR listing including two black males, one black female, two oriental males and three white females.

The NIDR EEO Counsellor/Council Member is presently in the process of conducting meetings with groups of employees to communicate and explain his role as well as general EEO principles and concepts. Groups consist of supervisory and non-supervisory employees represented by each of the NIDR EEO Committee members and are organized and convened by them. Additionally, the NIDR Director meets on a regular basis with the Personnel Officer and the Chairman, NIDR EEO Committee.

Both on-the-job and outside training continue to be provided for those minority employees selected earlier for the Institute's Upward Mobility Program with promotions being processed as merited and indicated by individual progress and growth.

With regard to NIH-wide Upward Mobility programs, 14 employees are presently attending classes at the Upward Mobility College, and recently the Institute identified six potential employment situations for prospective STRIDE candidates.

Dental Research Institutes and Centers Program

The Dental Research Institutes and Centers Program concluded its preliminary phase of development at the end of fiscal year 1972. The major objective of this program is to broaden and strengthen the scientific base which underlies the national capability to improve oral health. An important aspect is to develop new manpower resources by challenging scientists from medical, engineering, and graduate schools, as well as other university components. The institutes and centers are to provide for participation of multiple disciplines and to facilitate the collaboration of a wide range of biological, physical, and social sciences in the study of oral health problems. In addition to interaction with components of the parent university, the institutes and centers should establish mutually beneficial relationships with other regional resources and with other institutions, both national and international. The progress of the five dental research institutes and centers, which have been in existence for five years, has been most laudable in meeting these objectives.

Each institute and center has established a stable permanent staff, including many scientific personnel who were not previously engaged in dental research. These investigators have developed many collaborative projects, not only on an interdisciplinary basis within their institute, but also with many investigators throughout the country and overseas.

The existence of the institutes and centers has already had a significant impact on dental education. Institute staff hold joint appointments to academic departments representing their basic field of competence. Institute scientists are encouraged to participate in educational activities, and they present seminars, give occasional lectures, and engage in other limited informal teaching. Needless to say, these activities have added to the strength of the dental faculty in the respective universities. Also, the existence of the institutes and centers has provided more of an opportunity for students to gain experience in research. In turn, this exposure has stimulated students to pursue careers in dental research.

The experience of the first five years has shown that success is primarily dependent on the active support of the university administration, the leadership of the director, the scientific excellence of the research staff, the establishment and maintenance of a suitable environment, continuing program evaluation and modification as indicated, and reasonably stable financial support.

Another major factor contributing to the effective development of these institutes and centers has been a continuing self-surveillance, and a parallel system of periodic review by NIDR staff and Advisory Committee. During 1971, four of the institutes and centers submitted competing renewal applications, and each institute was reviewed comprehensively by a site visit

team, the Dental Research Institutes and Special Programs Advisory Committee, and the National Advisory Dental Research Council. In addition to this review for the next five years of support, the institutes and centers received periodic progress reviews during the first five years of operation. This pattern of continuing evaluation served to assure the development of the institutes and centers as broad, interdisciplinary, university-based complexes with adherence to high standards of scientific merit and fiscal accountability. Each recipient institution is responsible for judicious management and for developing a program consistent with the concept of dental research institutes and centers. Furthermore, each sponsoring university has an institute policy committee to guide the activities of the institute in accordance with university and NIH policies. A scientific review committee is also available to each institute for overseeing the quality and cohesion of the total scientific effort.

The NIH-university partnership role has proven to be most effective. Evaluations of the institutes and centers, based on the professional judgment of site visit ad hoc consultants and members of the Dental Research Institutes and Special Programs Advisory Committee and the National Advisory Dental Research Council have been given to the responsible university officials, and they have been most receptive and grateful for the analysis of their strengths and weaknesses.

At its September 1971 meeting, the Dental Research Institutes and Special Programs Advisory Committee, in addition to reviewing the competing renewal applications, discussed the scope of surveillance for the second five-year project period. Items such as the frequency of site visits, the partnership role, and the focus and range of research were discussed.

The responsible university officials from the institutes and centers were invited to the February 1972 meeting of the Committee to discuss the initial developmental period and procedures for continuing evaluation during future project periods. Their input was candid and constructive, and, accordingly, contributed significantly to the NIH-research institute relationship.

In response to NIDR's five-year plan, "Oral Disease: Target for the 70's," the five institutes and centers will continue to strengthen existing programs and initiate new efforts in the targeted areas.

Information Office

The growing "consumerism" movement in this country is making itself felt in the health field. A Presidential Committee on Health Education is currently examining what the various Federal agencies are doing to inform the public how it can improve and maintain its health. The White House has also established a Consumer Products Information Center, an important concern of which is the dissemination of health information. NIDR's pamphlet, "Research Explores Plaque," has been selected by the center for inclusion in its quarterly consumer products information index, stimulating a large volume of requests for the publication.

In addition, DHEW this year is initiating a consumer information series of publications. Dental care is one of the four subjects selected for the first of these publications. NIDR and the Division of Dental Health are jointly involved both in drafting the pamphlet and in underwriting its production costs for issuance by the Department.

Current interest in preventive activity is finding expression in many forms. The NIDR Information Officer is participating in a multi-organizational project to design and implement a national health education program to help prevent periodontal disease. She is also serving as a consultant to a consumer group that is seeking to develop a national health education program in preventive dentistry.

The public's increasing concern with oral health problems is further reflected in the growing number of inquiries received by the Information Office. Over 7,600 inquiries were received this year, representing a 31 percent increase over FY 1971.

The spectrum of activity of the Information Office includes not only a multi-media program directed to the general public but also communications with the professional and scientific community. Thus, for example, of the 167,856 pieces of literature distributed this year, 36,700 were included in a special mailing to dental students. Illustrative of the diversity of distribution, publications were provided to the Society of Nutritive Education; to the 2nd ADA Conference on Practice Administration, emphasizing prevention; to the Walter Reed Army Hospital's dental program; to the Connecticut State Dental Association; to the dental health unit of the City of New Orleans; and for the Iowa diabetic detection drive. Twelve hundred copies of "Research Explores Plaque" were also provided on request to the U. S. Information Agency for use in ecological and life sciences book exhibits to be circulated in more than 20 countries worldwide.

Exhibit showings arranged by the Information Office similarly show a diversity of audience interest. During the year, exhibits were shown at meetings of the American Dental Association, the American Society of Metals, the Chicago Dental Society, the American Society for Microbiology, the Association for Supervision and Curriculum Development, and the National Science Teachers Association. The latter two meetings were staffed by Information Office personnel.

This broad range of interest is also evident in the types of publications that carried news items from NIDR during the year. They include Changing Times, Chemical and Engineering News, Harvest Years, Family Health, Dental Survey, Dental Hygiene, and the Journal of the Academy of General Dentistry.

In addition, a variety of services, ranging from arrangements for interviews with NIDR scientists to provision of data and illustrations, were furnished by the Information Office. Recipients of these services include Monitor, the official publication of the American Psychologists Association; Science; the college textbook Health Science; Infectious Diseases; Drug Research Reports; New York Times; Science and Vie; the Louisiana Pharmacist; and

Honeywell Information Systems. An Information Office representative also helped to staff the press room operations at the IADR meeting to facilitate media coverage of Institute and grantee papers.

Through its "News from NIDR," "Research Capsules," and regular contributions to the Federation Dentaire Internationale Newsletter, the Information Office calls the attention of dental editors and science writers to selected research news items. "Abstracts from NIDR Scientists" are prepared and distributed on request to dental scientists throughout the United States to keep them informed of Institute activities. A large mailing list is involved for making available Institute scientific reports to dental researchers outside the United States. Also, through the cooperation of the Pan American Health Organization, reprints of clinical interest are mailed to 100 Latin American dentists.

As part of the joint NIDR-ADA career orientation program, a paperback was published this year, under grant support, in the Pyramid Publication's "World of Science" series. Written by Lawrence Galton, the book seeks primarily to convey to high school students the scope and challenges of dental research. Copies have been sent to some 73,000 science teachers, as well as to science writers.

The book, "Laboratory of the Body," is a companion to a film with the same title, produced in 1969 under grant support and close supervision of the Information Office. Although intended for science-oriented high school students, it has also been shown to general audiences on television and is regularly used by several dental schools for showing to their students and in their recruitment efforts. According to the latest report from the Modern Talking Picture Service, distributor of the film, 1,931,119 persons have seen the film as of March 31, 1972. This is exclusive of dental students and the television audience. The film has won two awards: Gold Medal from the Atlanta International Film Festival and the Golden Eagle from the Council on International Nontheatrical Events.

The series of five colorcasts describing some of the research conducted and supported by NIDR, produced by the Information Office in cooperation with NBC-TV in Washington in 1970, have been shown in their entirety to date in 11 major cities. Additionally, during the year, one of the programs was repeated twice in a major city and another program in the series was telecast individually in another city.

A vigorous effort is made to have an NIDR representative interviewed every month during the intermission period of the weekly program on radio station WGMS, sponsored by the Library of Congress. During the year, 12 such interviews were scheduled. Arrangements were also made for a guest appearance on a local television program.

The pamphlet on canker sores and other oral ulcerations was revised, as were two leaflets dealing with research opportunities, and the special dental research award program. Similarly, the graduate training list which appears in the Journal of the American Dental Association was updated. New publications include "Improved and New Biomaterials to Advance Dental Health" and

"Research Interests of the Extramural Programs of NIDR." Six publications, including the Dental Science Handbook, were reprinted.

A major expenditure of Information Office staff time is on internal reports and the requirements of specialized audiences. Such internal reports include NIH weekly and monthly reports, research and program highlights, opening statements to Congress, special reports to Congress on particular segments of the Institute's program, the NIDR segment of the DHEW annual report, Presidential messages, and numerous other periodic and ad hoc reports. In addition, the Information Office this year answered 7,626 inquiries; developed 1 new exhibit (on biomaterials), and exhibited at 6 meetings; distributed approximately 167,856 pieces of literature; prepared 84 press items, summaries, releases, features, and announcements, including a special article on plaque for house organs (with a potential audience of approximately 13 million), and 6 "Search for Health" columns; 92 internal reports; 1 speech; 4 radio spot announcements; arranged 12 radio interviews, 1 television interview, and 15 showings of NIDR-NBC program series; prepared one new pamphlet and flyer and revised one pamphlet, two leaflets, and one article; and reprinted six publications. The Office also arranged orientation programs and tours for approximately 77 visitors; processed 143 manuscripts and 63 abstracts as the NIDR clearance center; and prepared the NIDR component of the "NIH Annual Bibliography" and the "Professional Staff of NIDR" publications.

Office of Collaborative Research

In the middle of the fiscal year the National Institute of Dental Research was one of the institutes accorded contracting authority under the NIH decentralization plan. The Office then assumed for NIDR contracts all the functions previously carried out by the NIH Office of Contracts and Grants, including their negotiation and execution. To meet these additional responsibilities, the Office was reorganized both organizationally and functionally.

Organizationally, the position of contract operations officer was abolished and a contracting officer was appointed. All OCR personnel were made directly responsible to the chief. Two additional part-time clerk-stenographers were recruited, one of whom serves primarily as file clerk. Thus we have been able to change the entire filing system, bringing it to a much higher level of efficiency and making it consonant with the central NIH filing system. A manual of internal procedures was written to standardize operations within the Office. Similarly, a manual of policy and procedural announcements was instituted to clarify and standardize contracting procedures throughout the Institute. An additional contract specialist trainee was added to the staff, so that the Office now has two fully qualified contract specialists and two trainees.

Functionally, the NIDR's contracting procedures were modernized and professionalized. The form approach to the preparation of contract documents was rejected because it inhibits original thinking and leads to ambiguous contract terms. Requests for Proposals and contracts are all now individually drafted to meet any given requirement.

Further, NIDR contracts are now drafted in such a way that advance understandings with contractors on subcontracts, consultants and other foreseeable direct costs are incorporated. Advance agreements reached with contractors during the negotiation stage greatly reduce the administrative workload which otherwise would later devolve upon both the contractor and the Government.

In order to minimize the number of one-year contracts for continuing programs and thereby reduce heavy year-end workloads while at the same time providing a greater sense of project continuity, all long-range contract projects were surveyed to determine which could be funded on a multi-year basis. For the first time in the history of the NIDR contract programs, suitable projects were funded in that fashion.

"Competitive range" evaluation principles were also put into effect for the first time. Not only does this procedure bring the Institute into compliance with the procurement regulations and recent Comptroller General decisions, but it creates a competitive climate which appears to give the Institute the best contract for its money.

Several other measures were instituted to further good relationships with actual and potential contractors. Several schools have been visited for the purpose of explaining the contracting process and the mechanisms thereof to the faculty. These visits appear to have been mutually beneficial. Further, this Office initiated the practice of sending correspondence to the person signing the contract on behalf of the offeror, with carbon copies to the contractor's principal investigator. Contractor administrators have been very appreciative of this procedure because it prevents problems from arising when a person working under the contract attempts to bypass his own administration. This preventive step has saved both contractors and the Government time and money which otherwise would have to be spent in attempting to solve problems that would otherwise arise.

Office of Program Studies and Analysis

Collecting, analyzing and reporting data related to dental research continues to be the major activity of this Office. Aside from a few recurring reports, our greatest emphasis is placed on the dissemination of information in response to ad hoc spontaneous requests. Queries for information come from a variety of sources. While primary responsibility is to the Director of NIDR, a review of the "logbook" indicates that the requests are about evenly divided between NIDR staff members and the Office of the Director. Of those requests that do come from the OD, the vast majority are referrals from some other component of NIH or from outside NIH. Representative of the latter group of requestors was the Office of the Secretary of the Department of Health, Education, and Welfare, Congressmen, the General Accounting Office, the Office of Management and Budget, the National Science Foundation, the Science Information Exchange, the American Association of Dental Schools and the American Dental Association.

Of the many and diverse ad hoc requests responded to by our staff, the following are typical: Dental Research Training Projection, FY 1973-1976 for NIDR Special Emphasis Programs; Background Information for the AADS Committee on Research Manpower; Trainees and Fellows with a Dental Degree Seeking a Ph.D.; NIDR and NIH Priority Scores and Initial Review Group Approval Rates for Research Grants, 1967-1971; RCDA and Special Fellowship Awardees; and Relationship of Basic Science Departments to Dental Schools by Type.

In order to meet these many demands in a reliable and timely manner and though not yet completely functional, we are organized around a Data Unit responsible for the collection, storage and retrieval of data and a Reports Unit whose mission is the analysis of data and the compilation of reports. We are looking forward to a time when, with the proper acquisition and mix of personnel, this organization will be fully functional and coordinated in its efforts. Most of the problems related to space, equipment and the technical aspects have been or are capable of being solved. There is, however, a perennial problem over which we have little or no control, i.e., the collection of reliable data on matters of interest to dental research from outside the Institute. Our efforts to determine the projected need for dental teacher/investigators is a typical example of this deficiency. Advances have been made and will continue to be made to bolster this weaker aspect of our data base.

Two sizable projects this year have given us a new comprehension of the status of dental research in U.S. dental schools and in all institutions throughout the nation. The first of these, NIH Support to U. S. Dental Schools, FY 1971, displays the actual NIDR support to dental schools without the confusion of including that support which goes to the parent institution as in previous reports of this nature. The second, which will be published and distributed as Dental Research in the U.S. and Canada, FY 1971, has evolved over several years. However, as a direct result of the close liaison between our Reports Unit and the Science Information Exchange, it now has greater coverage and is much more accurate than ever before. Furthermore, it has attracted the interest of enough parties outside of the Institute to lead us to expect even more refinement in the future as the value of reporting projects is more clearly understood by the entire community of dental investigators.

Another and more familiar publication series from the Reports Unit, the National Institute of Dental Research Grants and Awards, Fiscal Year 1971, serves as a handy "desk reference" for data related to our own grants and awards. It is still the single most accurate and comprehensive source of such information available on an annual basis and preserves these data for subsequent years.

The Data Unit, as part of its long-range plan and with part-time help, has constructed a computerized record of NIDR-supported trainees and fellows. It is anticipated that this "core" will be expanded into a comprehensive dental investigator file. A further extension of this capability will be the computerization of our entire dental research grants file. The "spin-off" of our work so far has been the ability to provide our contractor with

a complete and updated mailing list of trainees and fellows for his use in conducting the NCI/NIDR post-training survey scheduled to begin this year.

The popular "green book," or Trainees and Fellows Supported by the National Institute of Dental Research and Trained During Fiscal Year 1971, is a recurrent publication compiled by the Data Unit. The inclusion of research project titles has made it a valuable placement tool for new investigators.

The coordination and compilation of the National Institute of Dental Research Annual Report (1971-1972), has been an interesting and rewarding experience for the Office. At the suggestion of the Director of Intramural Research, NIDR, with the permission of the Director, NIDR, and the Deputy Director for Sciences, NIH; and with the cooperation of everyone involved, a new format is being tried which promises to give the Report a new look and make it a more useful document for its readers.

Annual Report of
Associate Director for National Caries Program
National Institute of Dental Research

In October 1968, the Director, NIDR authorized formation of a Caries Task Force of leading scientists representing various phases of caries research and drawn from both within and without the Institute. Formally appointed in January 1969, this Task Force was charged with conducting a state-of-art evaluation of the caries field and with making specific recommendations for program activation.

In January 1970, Dr. Roger O. Egeberg, Assistant Secretary for Health, DHEW, announced that President Nixon had selected NIDR's plans for a National Caries Program (NCP) as a special health initiative, along with analogous programs in cancer and heart disease. A line item of $5,000,000 to implement this initiative was included in the President's Budget for FY 1971. Though conceived in 1968, the NCP became operational in fact only in March 1971, when this appropriation became available.

Program Management

Organization. Because it developed from ongoing programs of caries research at NIDR, the NCP at the outset comprised elements of intramural research, extramural grant programs, and collaborative contract activities. Simply coordinating three such semi-independent operations could not be expected to achieve the concerted effort declared as the principal mission of the NCP.

The way to a single management line was cleared in September 1971, when the Deputy Director for Science, NIH, approved the request of the Director, NIDR, to establish an Office of Associate Director for National Caries Program and to unite under it the three operational modes of direct research, research grants, and research contracts. A Caries Prevention and Research Branch was created by transferring the Disease Prevention and Therapeutics Branch from the NIDR intramural program; Sections on Biometry, Community Programs, Epidemiology, Field Trials, and Laboratory Studies were constituted. Similarly, a Caries Grant Programs Branch was created by transferring the Dentitional Diseases Program from the NIDR extramural program. Finally, the contracts operation was formalized as the Caries Contract Programs Branch.

Operation. Over-all executive management of the NCP inheres in the Associate Director, NCP, plus the three NCP Branch Chiefs. In its ordinary activities, the Caries Prevention and Research Branch operates in the traditional framework of NIH intramural programs, investigators being responsible to their Section Chiefs, who in turn are responsible to the Branch Chief. Staff of this Branch contribute importantly also to the Caries Contract Programs by serving as Project Officers. Everyday operations of the Caries Grant Programs Branch necessarily fall in line with policy and procedural guidelines for NIH Extramural Programs; accordingly, this Branch works closely with staff of NIDR's Extramural Programs. Similarly, the Caries Contract Programs Branch

maintains close liaison with the Office of Collaborative Research, a component of the Office of the Director, NIDR, for administering contracts. The Chief of the OCR serves as NIDR Contracting Officer and advises the NCP in matters of contract policy and procedure.

For program planning and development, in addition to day-by-day staff input, heavy reliance has been placed on a Caries Advisory Committee, a Caries Executive Committee, and a Contract Review Committee. The Caries Advisory Committee grew out of the original Caries Task Force and has functioned essentially as the brain trust of the NCP. At present it consists of 4 NCP staff and 11 outsiders. It conducts or sponsors state-of-art reviews of caries research as the basis for specific recommendations for program activation, deactivation, or change of emphasis; it reviews NCP progress and advises NIDR accordingly; it convenes groups of expert consultants as needed for special technical advice. The Caries Executive Committee consists of eight NIDR staff selected for knowledgeability in relevant areas. It was set up to provide the Associate Director, NCP, continuing in-house assistance in programming NCP contracts, in selection of areas ready for solicitation of contract proposals, and in identification of program areas needing development. The Contract Review Committee, consisting of 7 senior NIDR staff and 3 non-Federal members, was established to provide secondary review of all NIDR contract proposals and to make specific recommendations to the Director, NIDR, whether to award or not. Consideration has been given mainly to conformance with contract policy and procedure, adequacy of primary review for technical merit, probable value to program, and compatibility with budget.

Unless contracts are involved, projects engendered by investigators in the Caries Prevention and Research Branch are subject to approval in the traditional NIH intramural way by the respective Section Chief and the Branch Chief, if appropriate, they may be referred to the other Branch Chiefs and the Associate Director, NCP.

Research grant proposals naturally continue to be rated first for scientific merit by an NIH Study Section and reviewed secondarily by the National Advisory Dental Research Council. Assignment to the NCP is made in conference with NIDR extramural staff according to established criteria. In order to make the grant mechanism maximally responsive to the mission of the NCP, however, final decision to award has made increased use of the criterion of high program relevance, determined with Council approval.

Contract proposals are sought by the usual mechanism of issuing Requests for Proposals, which are prepared by NCP staff. All responses are reviewed first by the Caries Executive Committee for responsiveness to program objectives and priorities. Each proposal passing this stage is next reviewed according to standard criteria by a minimum of five experts; at least three of these (or not less than half) must be non-Federal. Reviewers' evaluations are then collated by the Caries Executive Committee, who prepare a composite recommendation and summary evaluation for consideration by the Contract Review Committee. Finally, necessary administrative action is referred to the Office of Collaborative Research.

Personnel Changes

Dr. William Rogers, Jr. and Dr. Louis Wachtel were appointed Chiefs of the newly created Caries Grant Programs Branch and Caries Contract Programs Branch, respectively.

Near the end of the reporting period, Dr. Henry Scherp retired as Associate Director for National Caries Program and was succeeded by Dr. James P. Carlos. Dr. Charles J. Donnelly was, in turn, appointed Acting Chief, Caries Prevention and Research Branch.

Dr. Ralph A. Frew was appointed Assistant to the Associate Director for National Caries Program.

State-of-Art Projects

The master plan for the NCP is inherent in the avenues to caries prevention. As a guide to program emphasis within this framework, several state-of-art projects have been sponsored; more are intended. Catalogs have been assembled of all the caries projects that could be discovered in the United States and Canada for fiscal years 1969, 1970, and 1971, as a measure of the total national effort against caries (NIDR supports about half). Workshops have been held on techniques for identifying oral bacteria and on behavioral impediments in preventive dentistry. Three two-day conferences of leading authorities have been convened: on phosphate physiology and caries prevention, to devise means for lessening human caries by dietary phosphates; on the role of human foodstuffs in caries, to guide dietary modification; and on comparative immunology of the oral cavity, to appraise the scientific basis for immunizing against caries. Much of the conference proceedings has been or will be published for the benefit of the research community.

CARIES CONTRACT PROGRAMS BRANCH

Research in areas requiring special efforts to attain the National Caries Program goal of preventing tooth decay are stimulated by requests published throughout the country. These requests explain in relatively general terms the needs of the Program, and prospective contractors are asked to submit original proposals designed to accomplish them. Emphasis is placed on practical research with targeted goals that can by achieved in a few years. Fundamental studies are supported only if they are designed to produce essential information for developing answers to the problem of caries prevention.

Contracts resulting from these Requests for Proposals are assigned to Project Officers according to their scientific specialties, i.e. nutrition, microbiology, clinical dentistry. The P.O. monitors the project and acts as scientific liaison between the contractor and the Program, but responsibility for performance and execution of the Workscope remains with the contractor. The role of the P.O. is to coordinate the individual efforts of the contractors with overall Program requirements, and to administratively assist the contractor in achieving his goal.

Contracts which have been in effect during the past year, and their significance to the Program are described below according to NCP Research Program Areas.

A. Modifying the Diet

1. "Evaluation of Cariogenicity of Snack Foods" (72-2039...Eastman Dental Center...$115,372). Approximately 25 human snack foods have been tested in vitro to establish their relative cariogenicity. Presently a nutrition survey is being conducted in a school in the Rochester, N.Y. area to ascertain the snack eating habits of junior high school students. In the future a clinical study will be conducted with students in the Rochester area in which snacks of low caries potential will be substituted for snacks normally consumed. Comparable studies will be conducted with rats fed snacks of low and high caries potential. This project will test the effectiveness of substitution of low cariogenic snacks for those of high cariogenicity in reducing the incidence of caries in humans.

2. "A Study of the Influence of Modified Diets Upon Quality and Quantity of Human Dental Plaque" (71-2376...University of Minnesota...$68,409). Approximately 130 dental students have subsisted on diets of low or high caries potential for a 4 day period at the University's Clinical Research facility. The amount of plaque produced during the period was quantitated. Students subsisting on high sucrose diets produced greater amounts of plaque. Presently methodology is being standardized for biochemical and bacteriological characterization of plaque samples. In the future, a potential anti-caries agent will be fed to determine how it influences the quantity and/or character of plaque. These studies will demonstrate the influence of sucrose on plaque formation (a precursor to caries development), and provide means of rapidly evaluating anti-plaque agents.

3. "Estimation of Caries-Producing Potential of Human Foods and Their Potential Role as Carriers of Possible Caries-Inhibiting Agents by Assays with Experimental Rodents" (71-2382...Harvard University...$34,156). One experiment using a periodic feeder has been completed. The feeding protocol and the equipment tested indicate that adequate nutriture can be provided in a periodic feeder that dispenses "meals" whether the "meal" is of high or low-caries potential. Presently, the heads of the rats are being evaluated for caries incidence. In the future the caries-producing potentials of human food-stuffs will be assayed. The successful development of this new assay system will provide a relatively quick and inexpensive means to determine the caries potential of human foods with or without caries-inhibiting agents.

4. "A Study of Trace Element Content and Dental Caries" (71-2381...Eastman Dental Center...$148,547). One hundred thirteen dentists have sent the contractor a total of 322 teeth from patients under 20 years of age, together with dental and childhood residence information. Trace element analyses have been performed on 135 samples of these teeth from different geographical parts of the United States with varying caries prevalence. Teeth from a low-caries area in Ohio appear to have a markedly elevated strontium content. Nutritional surveys are being conducted in communities with the greatest differences in caries prevalence. From this study it is hoped that a relationship may be determined between caries susceptibility and trace elements other than fluorides.

5. "An Analysis of Trace Metals from Colombia, S.A." (71-2384...Forsyth Dental Center...$49,539). Seventy-two soil and water samples from a low caries village and 79 from a nearby village of high caries prevalence have been analyzed. These data indicate that the levels of calcium, magnesium and vanadium are significantly higher in soil and water samples obtained in the low caries village. Analyses of samples of food, teeth and saliva from these villages are now being obtained. When the study is completed it is anticipated that there will be a greater understanding of the role of specific trace elements in preventing tooth decay in an environment which is naturally low in fluorides.

B. Combatting Cariogenic Bacteria

1. "In Vitro and In Vivo Tests of the Anticaries Efficacy of Certain Agents" (71-2332...Medical College of Georgia...$78,312). Assay of 21 potentially effective anticaries compounds provided by various pharmaceutical organizations has been completed. The test system involved eight caries related bacterial strains. Agents have been tested for their ability to inhibit microbial growth, in vitro plaque formation, and acid production. In vivo toxicity studies have been conducted in Norway white rats. Caries inhibition has been assayed through animal challenge with streptomycin resistant cariogenic Streptococcus mutans. In addition to suggesting which agents have greatest potential for caries prevention in the human, completion of this systematic survey will provide information relative to the validity of the chemo-therapeutic approach.

2. "A Study of Antimicrobial Agents Affecting Cariogenic Microorganisms" (71-2331...University of Minnesota...$49,260). The phosphoenolpyruvate (PEP): glucose phosphotransferase system has been characterized in Streptococcus mutans 6715. Transported hexoses phosphorylated at the C-6 position were dependent upon PEP. A similar glucose transport system was observed for Streptococcus salivarius and Streptococcus sanguis. Radioactive sugars have been used to study the ability of bacterial membrane fractions to concentrate various compounds and phosphorylated derivatives have been identified by standard enzymatic and ion exchange resin techniques. Knowledge of the unique membrane-associated sugar uptake systems of oral cariogenic streptococci will serve to give direction to the search for specific inhibitors of these microorganisms.

3. "Isolation and Purification of Microbial Dextranases" (71-2329... Beckman Instruments, Inc....$114,600). Enzymes with high specificity for degrading the complex polyglucan "dextrans" from cariogenic Streptococcus mutans have been isolated and purified. An enrichment culture technique utilizing, as substrate, insoluble polyglucans from several strains of S. mutans was employed to screen for those microorganisms best suited to produce the desired enzymes. Based upon the assumption that the complex polyglucans of cariogenic streptococci are structurally unique and that the dextranases presently available are not functionally specific for these "dextrans," completion of this study will provide new and potentially more effective anti-plaque enzyme systems. It is hoped that by removing or preventing the deposition of plaque, cariogenic organisms would not be able to attach the tooth surface.

4. "A Study of Immunization with Enzymes from Cariogenic Streptococci" (71-2330...Southern Illinois University...$61,259). Dextransucrases, levansucrases, and glycosidic hydrolases from Streptococcus mutans, Streptococcus sanguis and Streptococcus salivarius have been isolated, purified and assayed for their enzyme activities. Freshly prepared dextransucrases and other enzymes were used to immunize rat and monkeys via the salivary gland areas. Results suggest that salivary antibody has been induced in both animal systems as detected through inhibition of enzyme activity. Protective effects have been suggested from results of challenge experiments with cariogenic bacteria as well as from lowered caries scores in immunized animals. Completion of these studies will provide knowledge as to the value of the purified enzyme approach to immunization against caries. It is hoped that this may eventually lead to control of caries by immunization procedures.

5. "A Study of Local Immunization Effect on Experimental Dental Caries" (71-2333...Forsyth Dental Center...$64,949). The effects of locally induced salivary antibody to Streptococcus mutans has been studied in pathogen-free Spraque-Dawley rats. Salivary antisera from rats immunized with formalin-killed S. mutans 6715 were titered by agglutination of whole cells. Experimental and control animals were challenged with S. mutans 6715 and animals were monitored to determine numbers of persisting S. mutans and caries scores. Immunized animals gave rise to gamma A salivary antibody, they had fewer tooth colonizing S. mutans, and less caries than unimmunized animals. Completion of these studies will provide knowledge as to the value and limitations of the immunization approach to caries prevention.

C. Caries Susceptibility Tests

1. "Evaluation of Intraoral Test of Human Cariogenicity as a Model for Caries Studies" (72-2030...University of Alabama...$59,750). The potential usefulness of the Intraoral Cariogenicity Test (ICT) is being evaluated. This system involved incorporation of enamel slabs into acrylic flanges of prosthetic devices. The criterion of cariogenicity was the degree of demineralization of slabs maintained in the human mouth for selected time intervals. Incipient demineralization was determined by measuring microhardness changes. Comparative evaluations of slab versus natural lesions and microbial as well as biochemical composition of slab versus natural plaque have been undertaken. If evaluations demonstrate that the ICT is a valid model, it could be utilized to investigate the effects of the many variables thought to promote or inhibit caries development, and provide a rapid test of anticariogenic agents.

2. "Early Detection of Caries with Cystic Fibrosis Patients as a Model System for Longitudinal Study" (72-2045...American Dental Association... $37,449). Photographic equipment used for obtaining pictures of the intraoral condition of patients has been standardized with respect to reproducibility of color. Baseline clinical data for experimental and control groups is now being obtained. It is hoped that the use of the fluorescent technique employed in this study for disclosing early carious lesions will provide a rapid means of screening patients for incipient caries. Successful techniques for revealing early caries would expedite treatment thus preventing development of serious defects.

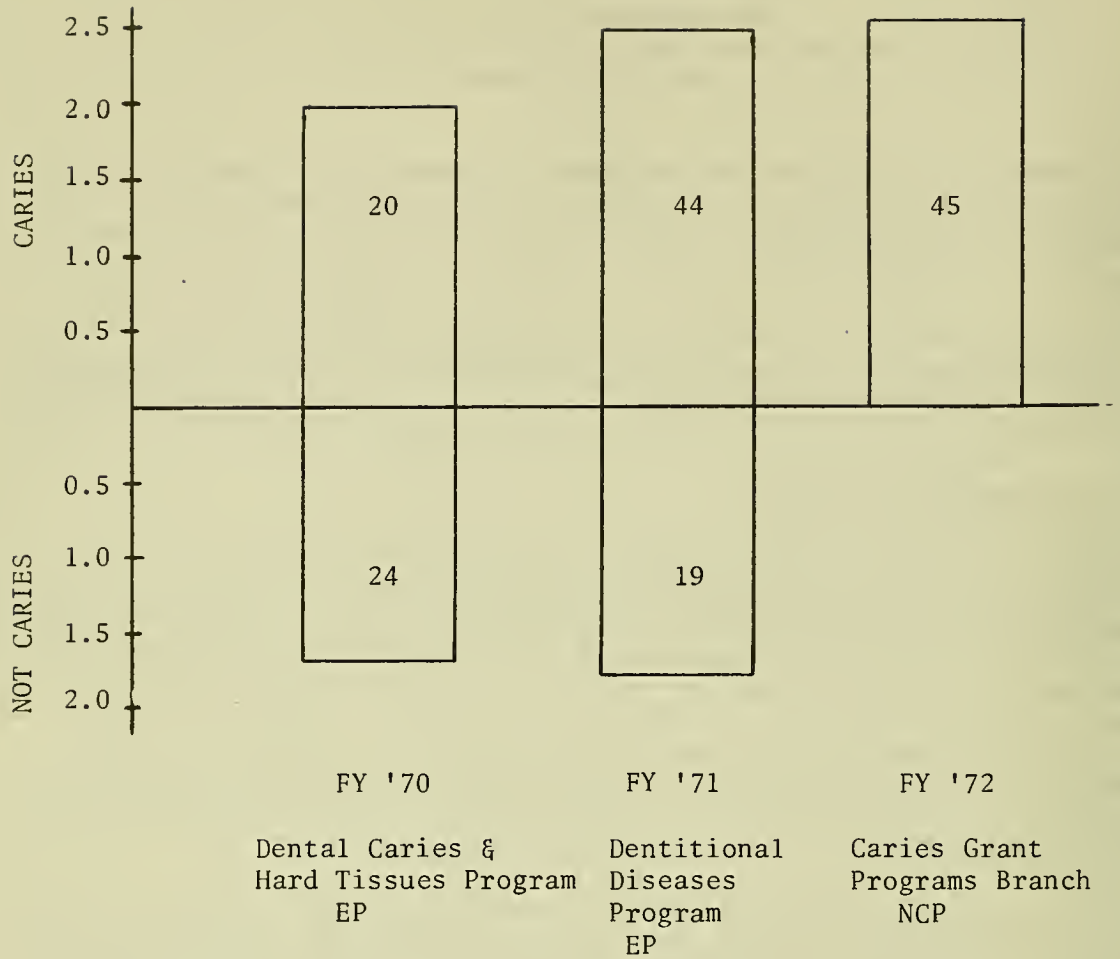
Caries Grant Programs Branch
National Caries Program
National Institute of Dental Research
Summary Statement

The Caries Grant Programs Branch (CGPB) administers the support of that research carried out by means of grants in the NCP. These grants span the spectrum of research focus, from the highly fundamental to the clearly applied. Through close work with consultants, with review groups of the NIH, and with individual applicants and grantees, the staff of CGPB attempts to develop a rigorously tested base of information concerning caries etiology and to facilitate the maturation of basic research findings to the stage where they are suitable for more targeted support through contracts.

Administrative Activities

Organizationally, the CGPB reports to the Associate Director, NCP, it coordinates its operations with those of the other NCP branches, and it is supported from the NCP budget. Operationally, however, the CGPB functions according to the policies and procedures of the EP, and its day-to-day management of grants resembles that of a regular extramural program area. Thus, after the Study Section review of new grant applications, the staff of the CGPB presents those that are assigned to it because of caries relevance to Council for final recommendations. The CGPB staff also periodically reviews for Council the activities and program plans of the Branch and analyzes for it the current grant support of caries research.

In 1970, Program Area I supported 44 research grants, of which 20 would be considered directly supportive to the NCP mission according to current criteria. From FY 1971 funds this Program Area supported 63 research grants, of which 44 concerned caries. Of the latter, 22 were funded by $900,000 of the $5,000,000 NCP "Add-On" of that year. Two of the 22 were assigned to other program areas. From FY 1972 funds the CGPB is supporting 45 grants, all focused on caries. Of these, 16, including one assigned to Program 4, were supported this year with $688,000 of the current NCP "Add-On." The increasing focus on caries in these programs and the effect of the targeted Add-Ons for caries research are shown graphically below in $ millions and numbers of grants. To maintain the CGPB at the current level will require the initiation of about $.9 million in new grants next year to compensate for normal attrition.



The initial FY 1970 Add-On enabled NIDR to fund immediately caries applications which previously had been submitted and approved. At the same time the NIDR plan to conquer dental caries through research was announced and received with enthusiasm. After a lag period, a significant number of scientists who are new to dental research, including some who are well known for the quality of their work, now are responding with innovative proposals of highest scientific quality. It goes without saying that every scientific area needs periodic refreshing with new talent to stay vital. The opportunity now exists to take advantage of the talent which is being proferred and build additional excellence into caries research.

It is anticipated that after the June Council has met the CGPB will have an accumulated backlog of 19 approved unfunded grant applications. The total

funds required to support these applications is estimated at $807,000. Two Council meetings in FY 1973 will add similarly to these figures. Funds to support new grants in FY 1973 are projected at $147,000.

It appears that the CGPB has a small funding base in relation to (1), the scientific talent that is available and could be focused on dental caries and (2) the uncertainty about the approaches to caries control that ultimately will lead to useful preventive measures. Since the base is small, jurisdiction by the CGPB of all grants that are relevant to caries would decrease their opportunity for funding. Because of this possibility, a considerable number of grants have been assigned to extramural program areas where there is a conceivable secondary interest. To present a coherent picture of caries research, it will thus be necessary in the following sections occasionally to relate CGPB activities to those relevant activities in other areas. Also, since a large fraction of CGPB projects are in their first year, some of these will be mentioned briefly so that the burgeoning thrust of caries research can be realized.

We believe that the reader will find very exciting new information about caries in the sections that follow, and will agree with CGPB staff that the research area has developed rapidly in response to increased funds.

As we did last year, we are attempting to describe each new development both with respect to the existing body of information in that area and with respect to possible application of the new development to control of caries. However, because the analysis based previously on host, dietary, and microbial factors is proving to be increasingly restrictive, we are describing research this year in six areas: (a) tooth resistance factors, (b) salivary factors, (c) microbial factors, (d) dietary factors, (e) tooth surface protection including topical fluoride, and (f) chemotherapeutics.

A. Tooth Resistance Factors

If the goal of a naturally caries-resistant dentition is to be achieved, it is likely that it will depend on obtaining detailed information on the processes of tooth formation, development and maturation, and on the physiological factors that modify these processes. For this reason the CGPB supports research on those developmental mechanisms that are unique to teeth and attempts further to relate research on teeth to that on bone growth and remodeling that is administered in other program areas.

It should be noted that little is known about the organic components of teeth or about their involvement in mineralization and that, with the exception of bone collagen, there is little ongoing research besides that cited below (and some in the extramural programs) in this very important area. At the UCLA School of Dentistry an investigator supported by the CGPB has determined through radiotracer techniques that the Golgi membranes of ameloblasts, odontoblasts, and osteoblasts are endowed with specific enzymes that are required for the synthesis and sulfation of the carbohydrate moiety of glycoproteins and mucopolysaccharides. These molecules then are transported through the cell wall to control the formation of, or be incorporated into

enamel, dentin and bone. At Northwestern University Medical School, another biochemist supported by NIDR has found that acidic glycopeptides are covalently bound to dentin collagen and postulates that these may serve as nucleation sites for the epitactic nucleation of calcium ions. It is interesting in this regard that the powerful bone induction principle isolated by NIDR-supported research at UCLA School of Medicine from demineralized bone has been found to be very sensitive to agents that modify its spatial dimensions or its structure.

At the University of Illinois College of Dentistry a histologist supported by a Special Dental Research Award is studying changes in tooth matrix formation and changes in tooth development caused by physiological insults to the ameloblasts and odontoblasts. The model system which is being employed in these studies is the response of the continuously growing incisor in the rat given brief overdoses of fluoride or strontium. This investigator also is studying changes in odontoblastic processes that lead to the development of sclerotic and peritubular dentin that retard the progression of dentin caries. These are important studies both because we do not understand the mechanism of formation of sclerotic dentin which is often found by the practicing dentist to have arrested an active lesion, and because we do not yet understand the relationship between hypo- and hypermineralized enamel and caries susceptibility. It should be added that we also do not know why caries spreads laterally at the dentino-enamel junction and, often extensively so, under pit defects and in interproximal cavities.

At the University of North Carolina School of Public Health a CGPB grantee is evaluating: (1) the benefits to children, and (2) the problems in distribution when the daily supplement of fluoride is supplied in tablet form by the schools. Initial results from this study indicate that tablet supplementation on a regular basis during the years of tooth development will prove to be a suitable alternative to water fluoridation. At the University of Antiqua, in Medellin, Colombia, a CGPB grantee is evaluating salt as a vehicle for fluoridation for the hundred million people of the world who do not have access to municipal water supplies. In 1965, salt fluoridation was started in two Colombian towns. After five years of fluoride exposure, the "def" and "DMF" scores for children in these towns now have been found to be as low as those in a Colombian town using fluoridated water and in a control town in the United States where the benefits of water fluoridation have been carefully measured. Though the possible toxicity of fluoride has been studied probably more than that of any other single substance, research in this area continues and CGPB is supporting an investigation at the University of Iowa School of Dentistry on the absorption of single doses of fluoride from the gut. In these investigations, carried out in a rat model, the fluoride levels achieved in the plasma are being studied as a function of time after the dose, age, presence of food in the gut, and other factors. The study has led to the findings that oral fluoride doses are absorbed by free diffusion in the stomach and jejunum but that fluoride is actively secreted from the mucosa into the lumen of the ileum and colon.

The Branch is supporting considerable research on the incorporation of fluoride into biological apatite while extramural programs having interests in bone formation, remodeling and resorption are supporting further basic studies on hydroxyapatite, the chemically pure form of biological apatites. At Lehigh University a Branch grantee is studying the nature, mechanism and rate of fluoride substitution in hydroxyapatite. He has found that the uptake of fluoride by some apatite is not a simple exchange for hydroxyl but involves replacement of unchanged water, complete recrystallization , and liberation of phosphate. He has established also that even when the fluoride activity in solution is several times greater than that in municipally fluoridated water, the uptake of fluoride by hydroxyapatite through mechanisms involving exchange is trivial. He believes that there may be unrecognized mechanisms of fluoride uptake perhaps involving monofluorophosphate. Also, this investigator has been studying the possibility that under anaerobic conditions apatites might be synthesized with a deficiency of oxygen through incorporation of reduced phosphate, such as meta-, pyro- and monofluorophosphate, in place of orthophosphate. He found that apatites with partial substitution of these ions could be achieved under laboratory conditions and had densities and other properties indicative of oxygen deficiency. Omission of an oxygen atom in the phosphate group in apatite increases the possible sites for fluoride substitution from 2 to 8 per unit-cell and markedly changes the uptake of fluoride from solution.

In research administered in the extramural programs a physicist at Princeton University has been measuring the rate of diffusion of various ions into oriented single crystals of hydroxyapatite. For all ions he found the diffusion coefficients to be low, suggesting that at biological temperatures bulk diffusion plays only a small role. This observation points to the importance of understanding surface and dislocation phenomena as controlling processes at biological temperatures. In addition, this investigator found that the migration energy for fluoride down the hexad axis was less than that of hydroxyl or oxygen ions. He interprets these results as suggesting that the role of fluoride in preventing dental caries cannot simply be that of blocking hydroxyl ion motion along this axis as has been previously postulated. Similar observations that bulk diffusion of fluoride into hydroxyapatite is extremely slow were reported this year from investigators at MIT.

At the National Bureau of Standards a physical chemist is studying the solubility of human enamel with goals of explaining the spreading subsurface demineralization that occurs in caries and the increase in caries resistance after teeth have been treated topically with fluoride. He has found through successive extractions of enamel with dilute phosphoric acid that tooth mineral contains a fraction that is considerably more soluble than hydroxyapatite. This observation leads to extremely interesting questions concerning the nature and the macroscopic and microscopic location of the more soluble phase. It is interesting that at Rensselaer Polytechnic Institute and at Case-Western Reserve University School of Dentistry grantees using the electron microscope to study the effects of acid and chelating agents on enamel find that the central core and outer shell of the crystals have different solubilities. Thus, in 0.001 N lactic acid, the central core dissolved in 5 minutes while the outer shell required well over 2 hours. These observations may

relate also to the mechanism of hydroxyapatite synthesis and to observations indicating that one or more intermediate phases are formed. In this regard, an investigator supported by the CGPB at SUNY has found initial formation of amorphous material and plate-like crystals when attempting to grow hydroxyapatite crystals from supersaturated solutions at room temperature. He proposes that these phases may be tricalcium phosphate and octacalcium phosphate.

Laboratory preparation of hydroxyapatite at physiological conditions of temperature and pressure, a problem which has resisted solution for many years, now appears to be close to solution. Though hydroxyapatite crystals of a size useful for physical measurements have been prepared at high temperatures and pressures, the product is different from that in bone. Now a CGPB grantee at the Polytechnic Institute of Brooklyn has made advances in this area using two techniques, slow diffusion of ions in buffered gels and slow increases in calcium and phosphate concentration through use of a Soxhlet apparatus. With these techniques he has been able to obtain crystals up to 0.08 mm in length, which, though marginal in size for use in x-ray work, are several orders of magnitude larger than those found in enamel. In addition, this investigator has obtained preliminary results indicating that hydroxyapatite of very high crystallinity can be obtained through a process in which phosphate ions are slowly released by the enzyme alkaline phosphatase acting on either nitrophenyl phosphate or β-glycerophosphate.

As was mentioned above, considerable research that is relevant to tooth mineralization, for instance on collagen structure, is supported in other program areas of the Institute. In order to round out, in part, the picture of Institute support of the area of mineralization, the progress of one of these areas will be mentioned. At Case-Western Reserve University a team of polypeptide chemists, physicists and theoretical chemists is attempting to establish the metabolic significance of the structure of collagen. One of the approaches of this group is to study in solution the structure and properties of polytripeptide models for the polar, non-polar, and hydroxyproline-containing regions of the collagen molecule. These models of specific areas of the collagen molecule are being examined with sophisticated instruments, such as laser Raman spectroscopy, to obtain information on allowed structures, inter- and intramolecular bonding, and superfolding of polypeptides. Recently this group has confirmed rather revolutionary new concepts concerning the extended charged coil form of charged polyamino acids in solution and has found, in addition, that dispersion forces are a major stabilizing factor for this form. The Case-Western Reserve team suggests that these concepts indicate that the conformation of the hydroxyproline region will be highly responsive to the chemical environment and to mechanical deformation and suggests that these interactions could play a fundamental role in the initiation of calcification.

Salivary Factors

In addition to the possibilities mentioned above for increasing host resistance to caries through amplification of the protective phenomena displayed by teeth, other possibilities exist in the bacteriocidal, tooth pellicle forming,

and immunity systems of saliva. The CGPB is providing funds to initiate research at the University of Nebraska on the antibacterial, thiocyanate-mediated peroxidase system of saliva and for a search for a suspected thiocyanate-requiring system that would be active under the anaerobic conditions of the caries lesion. Funds are being provided, also, to the A.D.A. Research Institute in Chicago for a program that is just getting under way to investigate a largely unstudied group of salivary proteins that migrate to the cathode during electrophoresis. One of these proteins is salivary lysozyme, which may act as an adjunct to local immune reactions that could be important in periodontal disease as well as caries. Other proteins in this group are thought to contribute to the pellicle that coats the surface of teeth.

The CGPB also is supporting two groups that are investigating the activity of salivary antibodies against cariogenic microorganisms. One of these, at NYU School of Dentistry, is surveying the incidence of specific immunoglobulin antibodies in the saliva of patients having different caries experience. A second, at the University of Alabama in Birmingham, is attempting to ascertain the biologic functions of antibacterially reactive antibodies in human saliva and to find the most effective procedures for enhancing specific immunity at the oral surfaces. The latter investigator has recently been able to increase markedly the yield of secretory immunoglobulin A from whole human saliva through use of gel filtration, has determined the sedimentation velocities of two major fractions, has determined the stochiometric composition of this immunoglobulin, and suggests that its association with a secretory component probably explains the fact that it does not form complexes with other proteins in the fashion of polymeric serum IgA.

At SUNY at Buffalo, a CGPB grantee has developed a radioactive assay for dextransucrase with which he has been able to demonstrate that antisera from rabbits immunized with specific strains of S. mutans inhibits up to 60 percent both plaque formation and the activity of the enzyme of these strains. Needless to say, the eventual goal of these scientists is to develop a caries vaccine. At the present time, however, many research hurdles remain to be overcome, including the seemingly simple one of accurately identifying the organism or organisms causing the disease.

Bacterial Factors

Through experiments with gnotobiotic animals it has been established that only certain plaque-producing microorganisms, principally Streptococcus mutans produce smooth surface caries. Though S. mutans is believed to be the chief cariogenic agent in humans as well, it is also believed that certain strains of this organism are much more pathogenic than others and that the natural form of caries probably is caused by a concerted attack by different microorganisms. Questions in this area could be answered in part by epidemiologic studies comparing caries prevalence with the particular species and strains of microorganisms found in the mouth. Unfortunately, the classification of strains of S. mutans, as well as the taxonomy of the species, still has not been clearly established, and the methods for identification and quantitative estimation remain tedious. Therefore, considerable CGPB support is being given to develop for the oral streptococci both an unambiguous classification

system and rapid procedures for enumeration of species in oral samples. Thus CGPB is providing support to an investigator at Ohio State University, who is studying the nutrient requirements, metabolic characteristics and colonial morphology of the cariogenic and noncariogenic oral streptococci. At the University of Florida another microbiologist is studying cell wall components, called teichoic acids, that distinguish each of the streptococcal strains on an immunologic basis. At the Florida Institute of Technology in Melbourne a third grantee is working out fluorescent antibody procedures for rapid identification of these strains. An alternative technique based on the observation that strains of oral streptococci are variably infected by different bacteriophages and bacteriocins is being developed by groups at the University of Alabama and the University of Maryland for classification and identification of these organisms.

Some of these new techniques, in addition to classical procedures, are being used to establish the degree of virulence and transmissibility of strains of S. mutans in human populations. At the University of Miami a large research team is investigating: (1) the ability of "labeled" organisms to establish themselves when innoculated in the mouths of volunteers, and (2) the prevalence and incidence of specific cariogenic strains in the mouths of caries-free and caries-rampant individuals and in population groups with widely differing dietary and socio-economic characteristics. In current studies on school children they report having found that: (1) S. mutans was present on both carious and sound tooth surfaces, although their numbers were usually greater in carious lesions, (2) S. sanguis was usually the most numerous of the organisms that form extracellular polysaccharide, (3) strains of S. mutans exhibited considerable variation in cariogenic potential in animals, and (4) S. sanguis does not induce caries in conventional hamsters, but in gnotobiotic rats some strains produced limited pit and fissure caries.

In addition to research on strain identification and the epidemiology of the cariogenic microorganisms, considerable support is being given by the Branch to studies of the ecology, pathophysiology and metabolism of these organisms. A biochemist at Rush-Presbyterian-St. Luke's Medical Center in Chicago is isolating and characterizing the extra-cellular enzymes liberated by the cariogenic microorganisms. Some of the enzymes convert food carbohydrates into sticky polysaccharides of plaque, others convert soluble glycoproteins of saliva into insoluble materials believed to contribute to tooth pellicle, while others attack surface components of the teeth and mucosal cells. Recently this investigator has established methods for obtaining relatively pure neuraminidase and other glycosidases from human saliva and has commenced studies on the levels of neuraminidase, β-galactosidase, hexosaminidase and fucosidase in rat saliva. At Forsyth Dental Center a large research team has been pursuing a number of studies of the ecology of oral microorganisms. One study has led to exciting concepts with ramifications outside the field of caries that may explain the functions of secretory immunoglobulins in controlling indigenous and infectious bacteria on all mucous membranes. Many organisms ranging from pneumococci, group A streptococci, and corynebacteria, to enteric gram negative bacteria have been reported by other workers to have surface "fuzzy-coats" which seem analogous to antigenic "M proteins" and which relate to the organisms' virulence. Through experiments in which the

fuzzy coat was removed the Forsyth group now has evidence that virulence of many organisms is associated with the ability to attach to epithelial cell surfaces. They have found, in addition, that treatment with specific M typing antisera prevents attachment of virulent strains to human cheek epithelial cells. Furthermore, they have found that salivary IgA, whose function has been obscure since it does not kill bacteria, fix complement, bind to macrophages or enhance phagocytosis, does inhibit both agglutination of streptococcal species and their attachment to oral epithelial surfaces. This group of investigators speculates, therefore, that the primary function of secretory IgA may be in preventing bacterial colonization, thereby affording specific protection to the mouth as well as to the naso-pharyngeal area and the gastro-intestinal canal of man.

In other research the group at Forsyth has been gathering evidence on the probable oral source of infecting organisms in subacute bacterial endocarditis. Alpha hemolytic streptococci, particularly S. sanguis, are recognized to be the most numerous organisms associated with this disease. Since these investigators found the organism in stool samples of only about 10 percent of the humans that they examined, but in all dental plaque samples, they feel that an oral source of the infectious organism is highly likely.

It should be emphasized that though a large portion of current research is focused on smooth surface caries caused by streptococci, other microorganisms are found in large numbers in root caries and pit and fissure caries. Thus, the Forsyth team mentioned above also has been studying the flora associated with human cervical caries and loss of alveolar bone. In teeth without enamel caries but extracted for periodontal purposes, they found that the predominant flora in the depth of the softened dentin was streptococci and filamentous organisms. Of 20 filamentous strains that were isolated, 5 were Rothia dentocariosa and 15 were Actinomyces, of which 2 were probably A. naeslundii, 5 were A. viscosus and 8 were not identified. Histological examination showed invasion of the dentinal tubules by diptheroids and filamentous organisms and lateral spreading between tubules. At the University of Michigan School of Dentistry a CGPB grantee using anacrobic culture techniques compared the streptococci, lactobacilli and veillonella species found in human plaque and in dentinal caries. Streptococcal strains accounted for 15 percent of the isolates from dentin but 30 percent of those from plaque. L. casei apparently made up 33 percent of the dentin isolates and 14 percent of the plaque isolates. Veillonella strains accounted for 16 percent of the isolates from either site. At the New Jersey College of Medicine and Dentistry also a Branch grantee using fluorescent antibody techniques has demonstrated L. casei (serologic group c organisms) deep in human dentinal caries.

The team at Forsyth and an investigator at the University of Miami School of Medicine have isolated an invertase from S. mutans. This development is significant since it indicates that this organism is not dependent solely upon glucosyl and fructosyl transferases for the utilization of sucrose. Since invertase has been identified in the β-methyl galactosidase transport system of E. coli, the finding of cell-associated invertase in S. mutans suggests that the mechanisms for sugar transport and the possible induction of

enzymes governing initial utilization of sugars should be studied intensively in this organism. Though dextransucrase of S. mutans has been considered to be a constitutive enzyme, the U. Miami scientist reports that he fails to find cell-bound dextran sucrase in glucose grown cells if the activity of invertase is taken into account. He further reports that the receptor site for dextran, which is involved in cell agglutination by sucrose, is heat stable and independent of dextran sucrase activity.

Several CGPB grantees are studying the structure of the branched polysaccharides synthesized by these enzymes. In work on these compounds it is currently reported from Villanova U. that the glucose linkages in broth dextran of S. mutans (E49) is 69 percent 1,6-like, 13 percent either 1, 2- or 1,4-like and 18 percent 1,3-like. From this data and other evidence, a tree-like structure is postulated for this polysaccharide with 1,3 linkages involved as branch points in chains of α-1,6-linked glucose. The investigator who reported these findings now is working on the structure and synthesis of levans. He has found that S. salivarius (SS2) preferentially uses sucrose for the production of levan rather than dextran but apparently does not utilize the levan to a significant extent as an energy source.

At the University of Minnesota a research career development awardee of the Branch has developed a simple way using doubly-labeled sucrose to distinguish and quantitate the levans and dextrans produced by these streptococci. Through use of this technique he found that all strains he examined produced both types of polysaccharide but S. salivarius produced mainly levans whereas S. mutans and S. sanguis produced more glucan than levan. He found also that cariogenic strains could degrade the levan produced by noncariogenic strains and that S. sanguis produces much more of the soluble glucan and as much insoluble glucan as does S. mutans. It is significant that the insoluble glucans of these organisms were found to differ widely in their resistance to hydrolysis in the presence of fungal and bacterial dextranases. At the University of Oregon another CGPB grantee has observed that the strains of streptococci living in plaque have different capacities to utilize levan as an energy source. Currently he is attempting to establish the relationship between this varied capacity and the cariogenicity of plaque microorganisms and of plaque itself.

The special metabolic features that allow certain microorganisms to be cariogenic while others even in the same species are not, is, of course, of deep interest to Branch grantees. At the University of Miami a scientist is investigating the significance of an extracellular protease which seems to be liberated only by cariogenic strains of S. mutans, and at Emory University a scientist is trying to establish the significance of a type of decalcification that seems closely similar to that occurring in smooth surface caries but which is obtained by exposing enamel to a protein dephosphorylating enzyme liberated by microorganisms implicated in caries. These observations of special enzymes, increased production of acid, and different levels of virulence in cariogenic strains of microorganisms become even more intriguing when one considers the observation of another grantee at the U. Miami. He has found that among the strains of oral streptococci that he has examined, all of those that are cariogenic seem to be infected with bacteriophage.

This investigator is currently attempting to cure and then reinfect streptococci with the bacteriophage while checking for loss and resumption of cariogenicity. If a causal relationship between phage and virulence can be established, it will provide a new way to "spotlight" those aspects of streptococcal metabolism that are responsible for cariogenicity.

(D) Dietary Factors

In this section we include components of the human diet that are utilized by, or directly affect, the cariogenic flora. Though the Dental Research Institutes currently are supporting a small amount of research in this category, the CGPB has not received grant applications with fundable priority scores that deal with diet. We feel strongly, however, that control is feasible through dietary modification. Thus sucrose could be partly substituted by less cariogenic sugars in the manufacture of sweetened foods. In other situations the sweetness of sucrose could be substituted by non-carbohydrate sweeteners. Also, non-toxic compounds, related to sucrose in structure, could be employed to block sucrose utilization by cariogenic microorganisms. Though some of the applied research requires special knowledge about food formulation, manufacturing, marketing and human metabolism of sucrose substitutes, there are still outstanding opportunities in this area for grant support for the independent investigator.

(E) Tooth Surface Protection

Through topical treatment there are various ways in which the tooth surface could be modified to increase its resistance to caries or could be coated to prevent adhesion by cariogenic organisms. In this section research is included on all types of surface treatment, such as modification of the surface by laser irradiation, protecting the surface with polymers, incorporating fluoride in enamel hydroxyapatite, and coating enamel with new layers of fluoride-containing compounds.

A grantee currently supported in the extramural programs now has considerable experience with children in the use of a thin coat of resin that is painted on the occlusal surfaces of the molar and bicuspid teeth and then polymerized in place with ultra-violet light. Few of these adhesive coatings have failed in three years and the reduction in the incidence of new caries in the pits and fissures of the teeth of the children has been extremely attractive. New research in this area is addressed to the question of whether sub-clinical carious lesions continue to develop underneath sealants, to the development of sealants that do not require prior conditioning of the teeth for adhesion, and to the development of procedures for sealing the smooth surfaces of the teeth. The CGPB is supporting two grantees who are carrying out research on non-polymerizing compounds that adhere to the tooth surface by chemical interaction. At Tufts University one of these scientists is studying a new series of phosphoramidate and phosphoric acid derivatives, while at Stanford University the other scientist has established that polyphosphonates adhere tenaciously to the enamel surface. As control agents these compounds might be incorporated in diets or in dentifrices.

Until recently dental scientists seeking better caries control through fluoride have used the working hypothesis that caries resistance was equatable to the fluoride concentration that had been achieved in the enamel surface. The rationale was that hydroxyapatite of teeth was converted to fluorapatite, a more acid-resistant compound. Recently, however, the use of advanced physical techniques has revealed that the mechanism by which fluoride reacts with the tooth surface is complex and that it changes in the presence of other ions. Today there is a greater appreciation for the inhomogeneity of enamel, for the complexity of the chemistry of biological apatites and for phenomena at the saliva-enamel interface.

Two CGPB grantees, one at the University of Iowa College of Dentistry and the other at Cornell College, Mt. Vernon, Iowa, have established by scanning electron microscopy and x-ray diffraction that treatment of enamel with SnF_2 leads to the crystallization of $Sn_3F_3PO_4$ and CaF_2 on the enamel surface. These investigators state that they found no chemical or x-ray diffraction evidence for fluorapatite in their studies and suggest that the formation of $Sn_3F_3PO_4$ might account for the reduction in caries in clinical tests with SnF_2.

At Forsyth Dental Center two CGPB grantees studying the removal of fluoride from solutions in equilibrium with hydroxyapatite report that three mechanisms seem to be involved: precipitation of fluorapatite, dissolution of solid hydroxyapatite followed by precipitation of fluorapatite, and non-specific processes that probably involve exchange of hydroxyl with fluoride ions or adsorption on the surface of the hydroxyapatite. The results of this study indicate that the rate of recrystallization is probably dependent on the rate of dissolution of hydroxyapatite and is decreased by the formation of a fluorapatite coating. The dominant process seems to be an initial precipitation of fluorapatite followed by recrystallization, apparently dependent upon surface-adsorbed fluoride. These investigators report that recrystallization is probably the most effective process for enamel fixation of fluoride in nonlabile form. They report also that this process is enhanced under acidic conditions which may explain the well-known greater retention of topical fluoride from acid than from neutral solution.

In other work, the investigators at Forsyth observed that a layer of CaF_2 is found when enamel is treated with either concentrated NaF or NH_4F. They found also that, in contrast to NaF treatment, the layer after NH_4F treatment is formed rapidly and is retained during prolonged washing. In subsequent clinical studies they found that a three-minute application of NH_4F (pH4.4) more than doubled the amount of fluoride remaining two weeks later in surface enamel, as compared with a similar treatment with NaF.

At the National Bureau of Standards also, an NIDR grantee has been attempting to establish means of increasing the rate of conversion of enamel hydroxyapatite to fluorapatite. Thermodynamic considerations have led this scientist to propose that hydroxyapatite in the presence of a pretreatment solution saturated with $CaHPO_4$ causes the precipitation of $CaHPO_4.2H_2O$. According to the proposal, this product in the presence of fluoride reacts to form fluorapatite. The optimal concentration of fluoride was determined to be between

0.1 and 0.2 percent. This investigator then used the theoretically-derived pretreatment solution in studies on human tooth enamel. Some samples were treated with saturated $CaHPO_4.2H_2O$ (pH2) and then exposed to NaF solution for 20 minutes. The increase in the amount of fluoride in the outer layer of the enamel was four times as great as that obtained by the pretreatment that is commonly employed, 0.05 M H_3PO_4 followed by acidulated phosphate fluoride.

At the University of Michigan a CGPB grantee is testing and examining physical models both for enamel demineralization and reactions of enamel with fluoride and other chemicals. His "fluorapatite" model assumes that when hydroxyapatite is exposed to a low fluoride concentration, a layer of fluorapatite is formed by isomorphous substitution of fluoride for hydroxyl ions on the surface of the apatite crystal and governs the rate of crystal dissolution. His experimental data is consistent with this model. At high fluoride concentrations, on the other hand, the experimental studies show that mainly CaF_2 with small amounts of fluorapatite are formed on the surface of hydroxyapatite and enamel. Recent results show that the formation of fluorapatite requires very high supersaturations with respect to CaF_2. Another interesting result arising from this physical-chemical approach to enamel surface chemistry is that phosphate pretreatment has an exceedingly strong influence upon the dissolution of hydroxyapatite. Indeed, the investigator reports that pretreatment of synthetic hydroxyapatite with 10^{-2}M phosphate at pH4.7 renders the material virtually insoluble to subsequent extraction by the same solvent. He states that this "false" solubility corresponds to an activity product as low as $1x10^{-155}$ whereas the thermodynamic solubility product for hydroxyapatite is about $1x10^{-116}$. The phosphate effect apparently requires that the hydroxyapatite crystals are relatively well-formed and has not been observed as yet with enamel samples. The relationship, if any, of this strong phosphate effect observed in vitro to the well-known anti-cariogenic effect of trimeta- and other phosphates in animal studies has not been established.

(F) Chemotherapeutics

Chemotherapeutics and enzymes incorporated in mouthwashes or other vehicles are a potential means of caries control for the general population. To obtain chemotherapeutics for anticaries use two possibilities exist: (1) identification and testing of agents among thousands of existing compounds that have not found use against other diseases, and (2) synthesis of new agents. Following the first approach the CGPB is supporting two microbiologists, one at the University of Michigan School of Dentistry and the other at Forsyth Dental Center, who are testing Kanamycin and Vancomycin for control of the flora causing caries and periodontal disease. These antibiotics dispersed in gels are applied to the teeth for several minutes on several days using close-fitting mouth guards. The investigators report in their initial studies that for two to three weeks after this treatment the cariogenic flora is depressed to extremely low levels.

On the other hand, the CGPB is supporting a scientist at the University of California School of Dentistry in San Francisco who is attempting to find inhibitors for dextran sucrase. Using a novel analysis based on the ultraviolet absorption of fructose this investigator is testing competitive inhibition by sucrose analogs such as 1-ketose.

The Branch also is supporting two scientists at the University of Tennessee Medical Units in Memphis who are using structure-activity concepts of modern medicinal chemistry to design agents to dissolve plaque and to inhibit the metabolism of cariogenic bacteria. Since it is likely that medicinal chemists through use of these techniques could suggest agents that would control caries through other mechanisms, the CGPB is actively seeking to interest this professional group in caries research.

In closing the first CGPB Annual Report, we would like to emphasize that whereas exciting research advances are being made and whereas some control measures already are being tested, ultimate solutions to caries suitable for all segments of our population are a number of years in the future. We feel that these ultimate solutions can only arise from a coherent body of information on caries etiology and pathophysiology. It is readily apparent in this report that scientists working with CGPB support are highly motivated to achieve this body of information. We are impressed both by their talents and by the progress that is being achieved even though their number in any particular field is small. Both wide-spread interest and considerable research momentum now have been achieved. We are deeply concerned, therefore, that funding of their research will be maintained until the final objective is achieved.

Report of the Caries Prevention and Research Branch
National Institute of Dental Research
Summary Statement

The Caries Prevention and Research Branch of the National Caries Program was organized and staffed in a manner which would allow it to capitalise on advances made in several areas of caries research. Although there are specific sections, research can and does focus around projects crossing section lines and involving scientists in other units of the Institute. Staff keeps in close contact and collaborates with scientists of other institutions working on common problems.

Emphasis is being given to the application and evaluation in community settings of those measures shown to be effective in preventing caries. Since preventive agents such as fluorides are less effective against pit and fissure than smooth surface caries, plastic sealant materials have been developed which seal these anatomical defects. The combination of fluoride and sealant is being evaluated in a community program for its effectiveness against these two main types of caries.

Considerable research effort is being directed at the development of more efficient and effective methods or agents of prevention. As these become available from our own or other laboratories, they will undergo animal, clinical and field testing to determine their effectiveness and practicability. Laboratory efforts are directed mainly at eludidating the etiological factors thought to be associated with human caries and the mechanisms by which control agents exert their effects. Considerable emphasis is being placed on bacterial mats-- both on the organisms present and their products-- and on methods and agents for preventing their formation or dispersing them to prevent cavitation. In addition, fluorescent antibody technics which would permit the quantification of bacteria in large numbers of plaque specimens collected in epidemiological investigations are being evaluated.

Epidemiological studies are seeking to identify the factors responsible for the increase in caries being experienced by populations which previously have been essentially caries free. One such population under study is the Yanamano Indians of Venezuela, many of whom live in villages isolated from contact with Western civilization. The effects of changes in diet and life style accompanying contact with civilization as well as the cariogenicity of the organisms are being explored. The importance of caries of the cementum is also being studied by the Epidemiology Section. For years, dentists have attempted to control these lesions by restorative dentistry but little information was available about their prevalence or nature. It is significant that root caries can only occur after the detachment of the epithelium by periodontal disease. Thus both processes-- one invading inward and the other downward can be active at the same time on the same surface. Recent research sponsored by the Branch suggests that root caries may affect nearly half of the adult population. The lesions are painful, difficult to restore, often result in exposure of the pulp and infection. It appears that the etiologic circumstances associated with root caries may be different from those related to coronal caries and that different methods of prevention may be required. In addition, investigations of root caries may help to clarify the etiology of periodontal diseases.

During the past year, the Branch's name was changed and it became a component of the newly formed National Caries Program under the direction of an Associate Director. Now the Branch, as the primary intramural caries activity, can coordinate more effectively its efforts with those of the other two components of the NCP which represent the caries research supported by contracts and grants.

To help researchers identify the various strains of streptococci found in the mouth, an atlas with colored photographs of streptococcal colonies (profile and top views) will be prepared. During the past year, a chapter on the epidemiology of caries and periodontal disease under the title "The prevalence and demographic characteristics of dental-deposit-induced diseases," was submitted for publication in a book,"Surface Chemistry and Dental Integuments."

The charge to The National Caries Program to prevent caries on a nationwide basis would benefit by the widest possible dissemination of information on current preventive procedures to the profession and public. Concepts of preventive practice were included in a chapter of a textbook for hygienists prepared by Branch staff. This chapter will be updated and reprints will receive wide distribution. In addition specific material on caries prevention for dentists will be prepared for distribution at a reasonable cost through the Government Printing Office. Staff members also have disseminated information on the prevention of caries to practitioners and students at professional meetings and schools in widely scattered parts of the country.

Report of the Biometry Section
Caries Prevention and Research Branch
National Institute of Dental Research
Summary Statement

The Biometry Section's first and primary role is one of service to the rest of the Branch. Members of the section consult with branch staff, other intramural scientists and investigators from other agencies and universities on design of studies. They perform systems analyses, assist in data collection, process data, and perform statistical analyses for both intramural and collaborative research projects.

To provide these services most efficiently, general systems are devised to handle projects of a similar nature. Research is conducted to determine the best set of data analyses for questions of a repetitive nature. These methods can then be made part of the general system. Once this is accomplished staff time can be devoted to interpretation of results from the general systems and analysis of data from unique designs.

In the systems area, procedures and analytic routines maintained for data from studies of root caries prevalence, caries prevalence, and microbiologic monitoring were modified and updated to analyze additional questions peculiar to particular studies. Routines were developed and computer programs written to convert and bring into the general system data from previous Division of Dental Health Studies, which were taken over by NIDR. It has become clear that the general tabular and analytic routines serve two functions. They allow an initial assessment of results or status without requiring special programming and they are easily modified for unique requirements of a specific study. This results in a considerable saving in staff time when compared with the time that would be required to write programs for every study.

Research on methods for analysis of caries clinical trial data has progressed in two areas. Columbia University has begun a collaborative effort to investigate various alternatives utilizing univariate analytic techniques. The Research Triangle Institute collaborated to develop a multivariate analysis of variance program and manual to be included in the general system. The availability of these methods tailored to caries clinical trial data will enable studies on the feasibility of partial dentition analysis for early detection of between group differences.

A visiting scientist assigned to the section conducted research in the area of malocclusion assessment. This effort has resulted in two reports. A numerical taxonomic method was developed for the classification of study subjects according to a reference population. This method simulates individual professional assessment by utilizing objective measurements. In addition, a study of agreement among orthodontists with regard to subjective severity assessments was completed.

This report is based, in part, on progress achieved during the year in Project Nos. NIDR-023 and NIDR-024.

Two clinical examinations for caries were analyzed in a study of the effect of dextranase as an anti-plaque and caries-inhibitory agent in humans. Differences among treatment groups, over a seven-month period, in periodontal and debris changes were assessed.

During the coming year the section will continue in its service role. It will assist in data collection; maintain, operate and update the general systems; provide consultation and systems analysis for new projects; modify existing programs or write new ones when necessary for unique projects; and carry out statistical analyses on study data. In addition, a data band and information retrieval system for caries contracts, grants, and intramural projects will be developed.

Appropriate analytic methodology identified as a result of current research will be implemented. This research will be extended to investigate the feasibility of utilizing techniques of multivariate analysis to detect differences among groups in caries clinical trials at an early stage, in the face of low control group activity, or on selected surfaces.

Report of the Community Programs Section
Caries Prevention and Research Branch
National Institute of Dental Research
Summary Statement

The Community Programs Section was established in the fall of FY 72 with the transfer of Drs. Horowitz, Heifetz and Driscoll from the Dental Health Center, Division of Dental Health to NIDR. The principal role of the Section is to engage in intramural research activities designed to evaluate public health methods or agents of proven efficacy for the prevention of dental caries. The feasibility of various agencies' responsible for dental health in their jurisdictions adopting a given program, should results be favorable, is a prime consideration in the decision of what methods or agents are evaluated by the Section. Emphasis is also given by the Section to designing programs that combine several decay preventive methods so that optimal benefits may be achieved. The Section thus was created and operates to conduct research on a practical approach to the prevention of dental caries.

Several studies that were formerly being conducted under the aegis of the Division of Dental Health were transferred to NIDR along with the personnel; these programs have formed the nucleus of the Community Programs Section. It is fortunate that the program and staff were able to be transferred with no loss in the continuity of these ongoing research activities.

The Section's study to determine the effects of acidulated phosphate-fluoride chewable tablets on dental caries (Wayne County, North Carolina) is proceeding smoothly. Children will be ending their third year in June 1972 of taking either one or two fluoride tablets daily on school days. Drs. Driscoll and Heifetz will conduct the first follow-up dental examinations from April 26 - May 9, 1972, to determine efficacy of the procedure. At that time, Dr. Roald Shern will obtain enamel biopsies of a random sample of children in the three study groups to determine their fluoride content.

Children attending the Seagrove School (Seagrove, North Carolina) will be examined during May 1972 to determine interim benefits to the teeth of children attending the school that has had its water supply fluoridated at 7 times the optimum (6.3 ppm) for four years. Students in grades 9-12 were transferred two years ago to a separate high school. During the examinations, a determination will be made of the feasibility of fluoridating the water supply at the high school.

During the week of May 22, 1972, children will be surveyed who are participating in a study to evaluate the ability of an occlusal sealant - bisphenol GMA - to prevent dental caries (Kalispell, Montana). Results of the first year follow-up examinations were analyzed during FY 72. A joint report with Dr. McCune (Extramural Programs, NIDR) and staff at the Dental Health Center is currently being developed.

This report is based upon progress achieved during FY 72 in Project Nos. NIDR 001, NIDR 002, NIDR 003, NIDR 004 and NIDR 005.

Dr. Horowitz conducted examinations after two years in a study to evaluate the self-application of a stannous fluoride-zirconium silicate prophylaxis paste among children in Santa Clara County, California. Dr. David Bixler of the University of Indiana is independently examining the participants. All radiographs from the second examinations have been diagnosed and data are presently being tabulated.

During FY 72, staff of the Community Programs Section published the following papers:

Occlusal relations in children in an optimally fluoridated community: IV. Clinical and social-psychological findings. Angle Orthodont. 41:189-201, July 1971. (Horowitz, H.S., Cohen, L.K. and Doyle, J.)

Comparability of study groups in clinical trials of caries preventive agents. J. Dent. Res. 50:1357, Sept./Oct. 1971. (McClendon, B.J. and Horowitz, H.S.)

Effect of school water fluoridation on dental caries: final results in Elk Lake, Pa, after 12 years. JADA 84:832-838, Apr. 1972. (Horowitz, H.S., Heifetz, S.B., and Law, F.E.)

Confidence intervals for percentage reductions. J. Dent. Res. 51:492-497, Mar./Apr. 1972. (Abrams, A.M., McClendon, B.J. and Horowitz, H.S.)

A few additional papers are in press and should be published during the remaining months of FY 72 or early in FY 73.

Staff of the Section continued to provide consultation during FY 72 to the Council on Dental Therapeutics, American Dental Association; The Food and Drug Administration; The Commission on Classification and Statistics for Oral Conditions, FDI; The Division of Dental Health; and The World Health Organization.

Plans are already underway to begin a new investigation in September 1972. An eight-year program will be initiated in all elementary schools in Nelson County, Virginia, to determine the cumulative effects of chewable fluoride tablets taken daily in school, biweekly mouthrinsing with a 0.1% solution of sodium fluoride, use at home of an "accepted" therapeutic dentifrice, the regular distribution of toothbrushes, including toothbrushing instruction and general dental health educational activities. Children in grades 1 - 6 will participate actively in the program, but evaluation will continue into junior and senior high school. Baseline examinations to determine the initial prevalence of dental caries will be done as soon as possible after school commences in the fall of 1972. Follow-up examinations to determine improvements in dental health from the combined regimen will be conducted approximately every two years.

During FY 73, final follow-up examinations will be conducted both in Kalispell and Santa Clara. These examinations will mark the end of three years of study in both investigations.

There are no definite plans at this time to initiate additional studies. It is possible that staff members may associate with investigations that are principally being planned by other, non-NIDR investigators.

Consultation will continue in FY 73 to various agencies and organizations. At the present time, Dr. Horowitz has a firm commitment to present three papers -- two in association with the forthcoming meeting of the FDI in Mexico City in October, 1972, and the other at the 1972 meeting (Chicago) of the American Society of Preventive Dentistry in July.

The Community Programs Section would be strengthened by being able to increase its staff. Another clinical field investigator would permit the planning and initiation of additional studies. The services of a public health advisor (dental hygienist) are required to coordinate field study operations, and to participate on occasion as an examiner in certain studies.

Report of the Epidemiology Section
Caries Prevention and Research Branch
National Institute of Dental Research
Summary Statement

The Epidemiology Section conducts field studies supported by laboratory investigations directed towards the clarification of the etiology of disease and toward its prevention and control. Laboratory activity focuses mainly on (1) the development and refinement of methods which will aid in relating the occurrence and distribution of dental caries to suspected etiologic factors, (2) screening potential preventive agents by characterizing them for their ability to adsorb on enamel, restrict enamel dissolution, inhibit glycolosis and bacterial growth, and (3) the testing of the cariogenicity of specific organisms. Field investigations seek to relate and determine the relative importance of potential etiologic factors to the prevalence and severity of caries in the human.

Caries of the root surface has been shown in selected populations to be considerably more prevalent than expected. In the groups examined, root caries increased with age from approximately 10-30 percent for the 20-29 year olds to 50-65 percent for the 50-60 year olds. The proportion of all adults aged 20 and over examined in these surveys with one or more root lesions ranged from 25 to 50 percent. It appears that if the problem of caries in humans is to be controlled, attention must be given to lesions affecting the roots as well as those which attack the enamel surfaces of the crowns.

The finding that specific streptococci are associated with smooth surface caries in animals needs to be confirmed in humans. However, the manpower and laboratory facilities for the large-scale field studies which would be necessary exceed our capability. It appears, however, that new fluorescent antibody technics could permit such studies. The preparation of S. mutans FA conjugates has recently been reported. Data concerning the performance of such conjugates suggests that through evaluation, improvement and production arrangements currently underway, that reagent quality S. mutans conjugates will be available shortly. Considerable time was devoted to the development of a system using new incidence light FA excitation for the evaluation of these FA quantifications methods and their application in epidemiological studies. Reagent quality conjugates and FA quantitation methods will allow us to analyze a large number of specimens rapidly permitting both exploration of relationships between the development of coronal caries and proportion of S. mutans and the monitoring flora changes during anticaries therapy.

This report is based upon progress achieved during FY 72 in Project Nos. NIDR 008, NIDR 009, NIDR 013, NIDR 016, NIDR 017, and NIDR 018.

The demonstration that plaque specimens collected in the jungles of Venezuela, placed and transported in a holding solution, reached NIDR in condition suitable for processing, opened the possibility of extending epidemiological studies to parts of the world where low or unusual patterns of caries have been reported. Of significance is the fact that S. mutans was frequently found not only in specimens taken from Indians living at the Ocoma mission where children were experiencing considerable caries but also in plaque removed from the teeth of Indians living in remote villages where evidence of caries activity was only rarely observed. The cariogenicity of a strain of S. mutans from a caries-free subject from one of the low caries villages is being tested in animals of known gnototiosis.

The potential usefulness of guanidines, amines and quaternary ammonium compounds in interfering with plaque formation and possibly disease was explored by first screening these compounds for their ability to (1) restrict bacterial aggregations on enamel, (2) adsorb on tooth structure, and (3) inhibit enamel dissolution. Of the compounds tested, Alexidine and three amines scored favorably on the tests given. Amines with a fluoride ion were quite resistant against enamel dissolution. Such screening tests suggest possible modes of action as well as identify compounds for consideration for clinical testing.

Data will be available for analysis on the durability and anti-caries benefit after two years of a plastic sealant material applied to pits and fissures of teeth in setting commonly used in public health programs. A study also will be underway to evaluate the effects on smooth surface and pit and fissure caries of the combination of sealant plus a short regimen of acidulated phosphate fluoride gel.

It is expected that the FA system for quantifying oral streptococci associated with coronal caries will become operational. This will permit the extension of epidemiological studies as well as the evaluation of the effects of anticaries agents on the oral flora. In addition, reagent grade conjugates should become available for strains of actinomycetes thought to be associated with periodontal disease and possibly cemental caries. Thus, it also will be possible to handle large volumes of plaque specimens taken from sound and carious root surfaces and to determine the proportions of various strains of actinomyetes. Since the data available suggest that root caries is a problem of some significance in our population, the epidemiological studies will be extended to explore relationships by surface between lesion and other factors such as recession, oral hygiene habits, periodontal status, pocketing and plaque.

It is expected that a study will be initiated to investigate the effect on the oral flora and on the incidence of caries of substituting invert sugar for sucrose in the crude panela which is the major source of refined carbohydrate for many Colombians. The investigation will be carried out in isolated villages in a mountainous area near Medellin, Colombia.

Report of the Field Trials Section
Caries Prevention and Research Branch
National Institute of Dental Research

This Section primarily conducts clinical or field trials of promising new agents or techniques for the prevention of dental and oral disease; designs studies which provide insight into the mechanism of action of agents effective in preventing carious lesions; provides consultative services for dental investigators in planning and interpreting clinical trials, and stimulates additional basic research efforts identified in the course of field trials.

Epidemiologic studies have been undertaken on the increased resistance to dental caries and the incorporation of fluoride (F) in enamel from topical F treatments or fluoridated water and the relation of caries-conducive streptococci to dental caries. There have been attempts to reimplant labelled strains of S. mutans and S. sanguis into the mouths of human beings, and a survey of the prevalence of caries of root surfaces has been initiated.

To measure any additional benefit which might be received from the uptake of high levels of F to populations in a fluoridated community, children in Stickney, Illinois, aged 9-12 years, received 25 repeated daily 15-minute topical applications by means of mouthpieces of a gel containing 2.6 per cent NaF, pH 3.2, 0.1 M PO_4. A statistically significant difference between treatment and control group means could not be demonstrated for either surfaces or teeth at the end of two years.

Approximately 550 exfoliated deciduous teeth were collected from children in the study and analyzed for F at various depths from the enamel surface. The mean rate of F loss was 5 ppm F per day at 5 μm from the enamel surface. The enamel continued to lose F for 8 months at which time a mean of 2,650 ppm F remained as compared to 1,000 ppm F for teeth collected from the control group. After 2 years enamel biopsies of the permanent teeth of 56 children in the treated group showed a mean of 4,490 ppm F at a depth of 1.37 μm, whereas 22 controls showed a mean of 3,102 ppm F at an equivalent depth.

It is planned to conduct clinical examinations at the end of a third year since the possibility exists that a significant treatment effect may then be demonstrated.

To determine whether differences in dental caries experience in groups of about 300 adolescents native to communities with approximately 1 ppm F and above or fluoride-deficient water supplies are related to the concentration of F in the outermost surface of the enamel of permanent teeth.

This report is based upon progress achieved during the year in Project Nos. NIDR-025 and NIDR-026.

Clinical dental examinations and enamel biopsies for fluoride content have been conducted in 7 cities in various parts of the U.S. Data have been evaluated for 3 cities with approximately 1 ppm F in their water supplies and 2 with fluoride-deficient waters. The mean dental caries experience (DMFS and DMFT) and mean total F concentrations for comparable weights of enamel removed by biopsy were calculated for the 5 cities. Between the 5 cities, higher mean F concentrations in enamel were not consistently associated with a lower mean dental caries experience for the children. The data, however, revealed a significantly greater caries experience and a significantly lower mean F concentration in the enamel (2,200 ppm F) of adolescents from Boston, Mass. than in fluoridated Danvers, Mass., with 1,700 ppm F in the enamel. The prevalences of caries in fluoridated Charlotte, N.C. and Stickney, Illinois were equal (DMFS = 4.5) but the mean F concentrations in the outer enamel were 2,700 and 3,100, respectively.

Within each city the subjects were grouped according to increasing concentrations of F in enamel but no uniform relation could be demonstrated between increasing concentrations of F in enamel and decreasing mean DMFS.

The presence of relatively high concentrations of complexed F and of aluminum were found in Stickney, Ill. (1 ppm F) where the subjects had the highest mean F concentrations in enamel as compared to the other cities with 1 ppm F in the water. Aluminum has been found to be the main complexer of F in drinking water and an important complexer of F in enamel.

It therefore appears from this preliminary analysis that the anticaries effect of fluoridated water is not determined merely by the concentration of F found in the outermost enamel, and that enamel F concentrations above 2,600 ppm F do not confer more protection than concentrations below 2,000 ppm F, and that the nature of the chemical bonding of F in enamel is important.

Data will be analyzed for 2 additional cities, Kalamazoo, Mich. (1 ppm F) and Midland, Texas (5 ppm F), and during the coming year it is expected that all data including those on trace elements will be analyzed in detail and interpreted for the preparation of a scientific report. Moreover, attempts will be made to initiate a study involving the prevalence of S. mutans in fluoridated populations demonstrating different caries experience.

Before attempting to demonstrate transmission of cariogenic organisms in humans, suitable methods of implantation must be devised. Six females were reimplanted once with their own labelled strain of S. mutans and another 6 with their own labelled strain of S. sanguis. Dental floss was used to implant cultures of the organisms interproximally on one side of the mouth only but sampling involved all arches. After

7 days, 72 per cent of the women harbored their organisms but after 150 days only one person harbored it in low numbers. Future plans include one more sampling after 6 months, and different studies on other population.

Clinical and radiographic examinations for the prevalence of root caries have been conducted on over 200 individuals. The initial evaluation on 55 persons is as follows:

Age	Mean No. active lesions per person	Mean No. restored lesions per person
30-39	0.51	1.31
40-49	0.44	1.05
50-59	0.53	1.46

There is little information on the prevalence of cemental caries in different segments of the population. The severity of the problem is likely to increase in the future as people retain their teeth for longer periods because of increased availability of dental care and adoption of improved methods for caries control. The development of periodontal disease in older patients is often accompanied by root surface caries.

Additional examinations will be conducted and all the data will be analyzed.

Assessment of the F acquired by tooth enamel under clinical conditions is important in the evaluation of topical F formulation and greater control of the in vivo biopsy technic (Brudevold) is desirable. The abrasive biopsy technic, therefore, was modified by controlling the surface area of enamel biopsied with a taped window, the polishing speed (900 rpm), and the pressure (200 gms.) applied to the felt cone carrying the abrasive slurry. The weights of enamel samples obtained in this manner were less variable on groups of extracted incisors with 10 operators than when no attempt was made to control such factors.

To determine if differences in dental caries experience for individual pre-school children relate to the F concentrations at definite depths in the outer enamel of deciduous teeth, clinical examinations were conducted on 280 children, aged 5.5 years in a fluoridated area and 384 exfoliated deciduous incisors have been collected for chemical analysis. This study will also make it possible to ascertain if children with caries-free deciduous dentition have higher F concentrations at 5 μm than those with carious lesions. During the next year an endeavor will be made to correlate the dental caries and F data.

In the 93 pre-school children there was 91% agreement between the presence of smooth surface carious lesions and the detection of one or more colony of S. mutans on culture. This relationship was found to be statistically significant. This survey substantiates previous studies which have shown an association between dental caries in the permanent dentition and S. mutans. It is likely that an even stronger association between dental caries and S. mutans than that observed could be demonstrated in longitudinal studies.

Report of the Laboratory Studies Section
Caries Prevention and Research Branch
National Institute of Dental Research
Summary Statement

The Laboratory Studies Section has focused on two main areas: (1) the pathogenic characteristics of the bacterial mats which form on the teeth of humans, and (2) the mode of action by which fluoride inhibits caries.

Research is directed toward the development of better methods both for the identification of streptococci and actinomycetes and for the determination of their pathogenic potential. Hopefully such information will lead to more precise methods of assessing levels of current caries activities.

In vitro models are used for assaying the effectiveness of various antibacterial agents, enzymes and other compounds in inhibiting the growth of "cariogenic organisms". In collaboration with investigators from another institution, the cariogenicity of organisms isolated from material removed from human teeth is being tested. An actinomyces-like microorganism isolated from the teeth of an institutionalized child, produced highly destructive lesions in the roots and periodontal tissues of mono-infected rats.

Antimicrobial agents have been shown to be effective in preventing caries in rodents. Studies now will be extended to determine the effects on the microflora of humans of various antimicrobials and of various regimens of therapeutic measures. Changes in bacterial population and activity will be monitored by periodically removing material from the teeth prior to, during and after treatment.

Fluoride is being administered in a series of investigations using rats to clarify the relationships between intake and uptake of F, its influence on the oral microflora and its influence on the occurrence and distribution of carious lesions. The variables being studied are, different concentrations of the agents and different time periods and methods of administration. It has been observed that animals receiving high concentrations of F prior to but not during the test period had higher levels of F in their enamel, but more caries than animals receiving no pretreatment but consuming relatively low concentrations of F in water during the test period.

These investigations will be extended using larger numbers of animals to confirm or deny these findings. Studies exploring the effects of F in food vs. F in water, time of administration and systemic vs. local application also will be extended.

This report is based in part, on progress achieved during the year in Projects Nos. NIDR 019, NIDR 020, NIDR 021, and NIDR 022

REPORT OF THE EXTRAMURAL PROGRAMS

NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1971 - June 30, 1972

by

Dr. Thomas E. Malone
Associate Director for Extramural Programs

The Extramural Programs completed the fiscal year with a number of significant accomplishments and a rather outstanding status with respect to our capability to fund new and competing renewal applications for research grants. On the latter point, it will be recalled that in FY 1970 only three new awards were made along with thirty competing renewals. In FY 1971 sixty-three new awards and thirty-two competing renewals were made. Of the sixty-three new awards, thirty-two were for the Special Dental Research Award (SDRA) program which was inaugurated in 1970 and reported on in the previous annual report when the first year's experience with SDRA was completed. Thus, although more than half the new awards for FY 1971 were for small SDRA grants, there was a tenfold increase in the number of regular research projects funded.

The funding pattern for research grants in FY 1972 was even better than that in FY 1971, which was described last year as a "vast improvement" over the previous year. Thus, it is expected that sixty-eight new awards and thirty-five competing renewals will be made this year. The outstanding feature here is that more than fifty of these are for regular research projects and about a dozen are for SDRA. This suggests that applications for the SDRA program have leveled off after the first year of the program during which an initial, large reservoir of newly-trained investigators applied for the program. One of the eligibility requirements for prospective SDRA applicants is that the applicant will have completed research training no more than four years prior to the time an application is submitted. This fact, taken with the previous statement concerning the initial depletion of the pool of eligible applicants, supports the prospect that there is now a plateauing of the number of applicants to the SDRA program.

In spite of this improved picture with respect to research grants, there is still considerable distress to be found in other aspects of this program. As in the case with all granting components of NIH, the problem of inflation imposes a heavy toll which is not always immediately apparent. The total number of research grants awarded this fiscal year will be about half the number funded a decade ago. Yet, the cost of this reduced number of grants is double the amount expended ten years ago. Various inflationary factors contributing to this situation are well-known and include increased costs

for salaries, equipment and indirect costs formulated for grantee institutions. To examine one component, the indirect cost rate for research grants now averages about 35 percent of direct costs. This outlay alone sharply reduces the number of research grants which can be made, particularly since more and more grantees are using salary and wages as the basis for calculating indirect cost rates. Without developing this thesis further, it is quite apparent that decidedly increased budgetary levels are needed if we are to offset the impact of inflation. At the moment, our increases fall far short of this essential goal.

Another factor which adds to the complexity of budgetary problems is the occurrence of insufficient fund actions. More than 100 applications, representing about $3 million, could not be funded this year for various reasons. Many of these proposals were inactivated because they had competed for funds during two fiscal years while others were in a low priority score range. Nevertheless, about a third of these applications with relatively good scientific merit will be carried forward for possible funding during the next fiscal year.

Prospects for funding competing research grant applications next fiscal year are very dependent upon events of the current year. The increased number of competing grants funded this year will significantly increase the noncompeting base for next fiscal year, thus reducing the allotment for competing applications. After the improved funding picture of the past two years, this means that a more stringent situation will prevail during the next fiscal year.

The challenge of training dental investigators through NIDR training grant and fellowship programs continues to be of great dimension and urgency. Training grants have been made to dental schools and other institutions for the past 14 years and it is apparent that they have already had a major impact in providing manpower for dental research. This research has in turn resulted in significant progress in the understanding of oral disease and the physiology of oral tissues. The magnitude of this base of information is well illustrated by the initiation of the National Caries Program which was dependent upon past accomplishments in caries research. Equally prominent initiatives seem imminent in other areas such as periodontal disease, oral ulcerations, and deformities of the face and mouth. Achievements in research would not have been possible without the important dental research manpower pool developed through the NIDR training programs. This fact can only be fully appreciated when it is considered that dentistry has lagged behind medicine not only in research productivity but in numbers of research-trained investigators. A quarter of a century ago, when the NIDR was created, there was only a handful of active investigators. Today they number more than 3000.

The increased emphasis on research resulting from training programs has additionally enriched dental school environments and contributed to a significant increase in the number of full-time dental school faculty. It is generally well-established that more than half of the teacher-researchers added to dental school faculties over the past decade were former NIDR trainees. The need for dental school faculty, however, continues to be an

acute problem. This ever increasing demand is further amplified by new directions which are emerging within the concept that dental care must be made available to all Americans. Faculties must be expanded several fold to produce the practitioners needed to offset the dental care crises. Investigators trained under NIDR training programs are therefore needed more critically than ever before as they instruct tomorrow's practitioners in the use of currently available preventives and techniques and as they discover through their own research more scientific and rational treatment procedures. During this period of uncertainty in the training area, it is especially important to cite the unique impact of dental training grants and to reaffirm their continued need in dental research and education.

During the current year increased attention has been given to the matter of better defining training priorities. In the past, NIDR-supported training programs were heavily weighted towards producing researchers in relevant basic science areas. Indeed, the original impetus for these training areas derived from applicants themselves in the academic community. This trend was reversed several years ago when the NIDR became more actively engaged in planning activities to assure training in areas of greatest deficiency and need. Although training in selected basic science areas has remained active, efforts to train individuals who can use scientific methodologies to pursue problems of clinical significance have intensified. These efforts have been subserved by a series of state-of-the-art workshops, drawing on expertise from the scientific community, to concurrently identify areas of high research and training priorities. These areas are specifically handled in the categorical area reports to follow.

As an adjunct to state-of-the-art assessments, plans are presently underway for joint meetings between staff, representatives from advisory bodies, and all program directors of NIDR-supported training programs. It is anticipated that these sessions will afford a unique opportunity for an informal evaluation of the overall status of the NIDR training programs, the extent to which objectives are being met, and their relationships to research needs as reflected in the NIDR Five-year Plan.

While research training costs continue to rise, the budgetary allotment for training grants has remained at a constant level over the past several years. It has therefore become increasingly difficult to initiate new programs in areas deemed to be vital to meeting dental research manpower needs. As pointed out last year, it has been necessary to displace certain types of training programs with those more responsive to current needs. It can be predicted that this trend will increase as evaluational activities such as those described above continue on a larger and more refined scale. During FY 1972, 86 training grants were funded at a cost of $5.2 million.

The fellowship and career development awards continue to be used by the NIDR to meet the manpower needs alluded to earlier but on the basis of individual selection through national competition. In contrast to training grants, postdoctoral fellowships provide a more flexible opportunity of training of individuals relative to choice of institution and preceptor. It would appear that the new approaches to reviewing these fellowships have been reasonably successful. The single review of regular fellowships conducted by our

training committee and followed by staff review is not only entirely satisfactory but can allow an earlier funding of approved applications. The review of career development awards by study sections can be expected to become more refined as these committees gain more experience with this type of award. 86 fellowships were supported during FY 1972 at a level of $1.4 million.

While five foreign grants were awarded in four countries during FY 1971 at a total cost of $100,585, only four foreign grants amounting to $74,320 were funded in FY 1972. With the decline of foreign research activities under the research grant mechanism, increased attention has been directed to the possibility of utilizing PL 480 funds for the support of research in "excess currency" countries. Dr. Zora Griffo, Chief, Developmental Biology and Oral-Facial Anomalies Program, visited Yugoslavia during the summer of 1971 and initiated fruitful contacts with scientists in Belgrade, Zagreb, and Ljubljana who were interested in dental problems. Subsequent to her visit, the special foreign currency program in Yugoslavia became restricted in use, and the prospect of further programming efforts seems dim. However, during the next fiscal year NIDR staff plan to visit Poland, India, the near East and other countries for the purpose of programming PL 480 research proposals.

Great impetus was given to programmatic activities of the Extramural Programs this year when $760,000 was released by the Office of Management and Budget for expanded support of research grants dealing with periodontal disease. Although discussed in greater detail in appropriate sections of this report, it should be mentioned here that this modest but important increase has already generated short-term and long-range plans and priority selection for the orderly development of rational preventive and treatment methods. While the Extramural Programs have supported research and training on periodontal disease for almost two decades, we have only recently established a programming effort that could be considered responsive to urgent national needs. From this standpoint alone, the report of the Periodontal Diseases Program area assumes high significance. Particularly notable have been the workshops supported over the past few years, the most recent being February 1972. In addition to providing a springboard for the orderly development of research on periodontal disease, a series of recommendations were made which are leading to accelerated efforts in applied research directed towards disease control, continued etiological studies, and, of highest priority, the development of methods for the control of dental plaque.

The Extramural Programs have always maintained responsibility for research and training in areas pertinent to oral cancer. However, in comparison to other program areas, support has been on a very modest scale. Research projects have dealt primarily with precancerous conditions, and virtually no training grants can be identified in which the intent is to produce researchers capable of pursuing studies in areas concerned with the etiology, prevention, and treatment of oral cancer per se. In a detailed report prepared this year by staff of the Soft Tissue Stomatology Program, it was found that research support for oral cancer was also minimal in other components of the NIH.

With the passage of the National Cancer Act of 1972, the National Cancer Institute was given a mandate for a concerted attack on all forms of cancer on a scale not attainable with resources provided in the past. Realizing the relatively low profile of research on oral cancer in the past, staff of the NIDR have met with program leaders of the NCI and discussed ways the NIDR could participate in the National Cancer Plan and specifically engage dental and other researchers in a vastly expanded attack on oral malignancy. It is gratifying that these communications have led to a cooperative arrangement wherein complete liaison now exists with regard to all activities bearing upon oral cancer. A major agreement, already in an active stage of development, is that a number of oral cancer programs should be established in association with existing and planned NCI cancer research centers. This cooperative venture between the NIDR and the NCI represents a unique approach to an important but neglected public health problem, and may well serve as a model for other inter-institute program developments.

As mentioned earlier with respect to training activities, Extramural staff have continued to organize and sponsor state-of-the-art workshops in pertinent research areas. These workshops, utilizing small groups of outside consultants, have now been well established as an excellent mechanism whereby past accomplishments can be accurately assessed and projections made for the future. They are viewed as a sine qua non requirement for program planning. In the area of oral-facial anomalies three workshops were held during the year. These included: (1) cleft palate: clinical research; (2) description of occlusion; and (3) training of clinical researchers in the region of the head and neck. In addition, a conference on clinical and research implications of oro-facial anomalies was held which focused on congenital and acquired malformations other than cleft lip and palate. The Periodontal Diseases Program area sponsored a workshop on immunological aspects of this condition and also convened an international panel of experts which made important recommendations for future directions of research on periodontal disease. The Biomaterials Program area held an ad hoc meeting with consultants for the purpose of identifying realistic goals and targets for the immediate future. Future workshops in this program area are planned on the subjects of biocompatibility and dental implants. The General Oral Sciences Program area held this year the second of two workshops on research and training needs in pain control in dentistry. Finally, a workshop in the area of viral diseases of the mouth is being planned by the Soft Tissue Stomatology Program area. Particular emphasis will be placed on the herpes simplex virus since findings to date strongly suggest new approaches to prevention and treatment.

As in the past, Extramural staff have been active in programming research in all areas of responsibility. In addition to the more routine type of programming visits with grantee investigators, staff accompanied the Director, NIDR, on visits to 27 dental schools in this country. From all indications these informal interactions have been highly successful as a medium of exchange between NIDR staff and the faculty and administrators of the institutions visited. Extensions of these contacts were made possible as staff attended national meetings including the International Association of Dental Research, American Dental Association, American Association of

Dental Schools, Federation of American Societies for Experimental Biology, American Cleft Palate Association, and the American Speech and Hearing Association.

In August of this fiscal year, the Caries Grant Programs Branch (CGPB) was established by the Director, NIDR, as one of a number of organization changes relating to the National Caries Program (NCP). The CGPB, formerly the Dentitional Diseases Program, is now constituted of only those grants which relate directly to caries. Mention is made of this organization change because it represents a unique arrangement within the NIH structure. The NCP, under the direction of an Associate Director, brings together the Caries Prevention and Research Branch from the Intramural Program, the CGPB from the Extramural Programs and a new Caries Contract Programs Branch to initiate, evaluate, and monitor research and development contracts. The grants branch was thus established organizationally outside the Extramural Programs, although functional relationships were maintained in such matters as management, grants policies, and other procedural details. The staff of the CGPB have participated fully in all extramural activities, and an assessment of this organizational structure at this point clearly indicates outstanding success in the coordination and integration of this branch with the targeted objectives of the National Caries Program.

Several staff appointments were made during the year in the Extramural Programs. Dr. Robert J. McCune was named Chief of the Biomaterials Program, and Dr. Zora J. Griffo was appointed Chief of the Developmental Biology and Oral-Facial Anomalies Program. Dr. McCune succeeded Dr. Anthony A. Rizzo, who had been Acting Chief, while serving also as leader of the Periodontal Diseases Program. Dr. Rizzo continues as Chief of the latter program. Dr. McCune came to NIDR from the Division of Dental Health where he was Chief of the Materials and Technology Branch at the Division's Center in San Francisco. Dr. Griffo succeeded Dr. K. Kenneth Hisaoka, who had been Chief of the program since 1966. Dr. Griffo came to NIH in 1969 as a Grants Associate and completed that program prior to joining NIDR in 1970 as a Program Officer in the Developmental Biology and Oral-Facial Anomalies Program. The Periodontal Diseases Program was also strengthened with the appointment of Dr. Raquel Halegua as Program Officer. Dr. Halegua came to NIDR from the Medlars section of the National Library of Medicine. Prior to that appointment she was a Research Associate with the American Dental Association. Mr. Nelson E. Lyttle, formerly Program Officer in the Dentitional Diseases Program, assumed responsibility for the Dental Training Committee as Acting Executive Secretary. Mr. Lyttle was a long-time Executive Secretary of the Dental Program-Project Committee and brings many years of experience to his new position.

The number of professional and other staff in the Extramural Programs is still not up to optimal levels. Although three program areas are without Program Officers, only one position can be budgeted at the present time. As was pointed out in last year's report, at least two professionals are needed for minimally effective management of each categorical program area. Our ultimate goal, however, still calls for three professionals per program area, each to handle either research grants, training grants, or fellowships.

In summary, the estimated dollar level of program area activities as of June 30, 1972 is as follows:

Program Area	Research Grants No.	Research Grants $(000s)	Training Grants No.	Training Grants $(000s)	RCA and RCDA Grants No.	RCA and RCDA Grants $(000s)	Fellowship Grants No.	Fellowship Grants $(000s)
(1)	45	2,645	12	783	4	82	12	124
(2)	58	3,205	8	452	4	100	14	189
(3)	62	3,413	23	1,145	6	134	14	203
(4)	32	1,453	9	570	2	43	3	49
(5)	25	994	10	594	8	173	11	142
(6)	30	2,127	27	1,616	3	68	5	60
	252	13,837	89	5,160*	27	600	59	767

*Does not include $110,000 Chairman's Grant.

(1) Caries Grant Programs Branch

(2) Periodontal Diseases Program

(3) Developmental Biology and Oral-Facial Anomalies Program

(4) Biomaterials Program

(5) Soft Tissue Stomatology Program

(6) General Oral Sciences Program

PERIODONTAL DISEASES PROGRAM

The Periodontal Diseases Program of the Extramural Programs of the National Institute of Dental Research has the principal mission of developing new knowledge of periodontal disease which may lead to prevention and eradication of this disease throughout the world. In attempting to accomplish this mission the program supports research and research training efforts in a wide variety of scientific disciplines through the mechanism of grant awards. Because of the complicated nature and multifactorial etiology of periodontal disease the research activities encompass a wide spectrum of biological science. Included among the projects supported in past, current, and projected efforts are very basic morphological studies as well as highly sophisticated biochemical and immunological studies.

During FY 1972, the Periodontal Diseases Program provided approximately $2.7 million to support 61 research grants, a substantial increase over the previous years' total. Part of this increase was due to the fact that several grants were transferred from another program area, but the main reason for the increase was the release of add-on grant funds specifically earmarked for periodontal disease research. With the new funds, it became possible to fund 18 new grants covering needed studies of both basic and disease-oriented nature. The program area also supported 11 training grants under which stipends were provided to approximately 45 trainees in the fields of microbiology, immunology, connective tissue biochemistry, and clinical science. In addition, the Periodontal Diseases Program supported 20 post-doctoral fellows including four research career development awardees.

Program Planning

Perhaps the most important developments in the Periodontal Diseases Program revolve around the release of new specific emphasis funds this year and the anticipation of continuing increases in research funds in the years to come. Expectations of these expanded financial capabilities have brought about significant efforts in program planning this year which involve the efforts of staff as well as the contributions of scientific leaders throughout the world. Earlier in the year a workshop planning meeting had already been held to begin the development of some specific plans for clinical research in the immunology area. At midyear a broad, comprehensive planning effort was begun and still continues. Involving, at the outset, outstanding researchers of international stature, a staff document was reviewed, and a number of suggestions made. Many of the latter are now being implemented.

Immunology Workshop, October 1971. A workshop to explore the possibilities of developing a coordinated clinical research program for studying the relationship of immune abnormalities to periodontal disease susceptibility was held early in the year. This two-day workshop consisted of a series of discussions by 18 scientists working in the fields of immunology, microbiology, pediatrics, hematology, and periodontology. These discussions dealt with the role of immune phenomena as regulators of the relationship between the oral flora and the periodontal tissues, and appropriate methods of study in humans. A summary of the proceedings follows:

It was felt that a discussion of the role of immune mechanisms in periodontal disease should deal with the immune system as a recognition system operating through both humoral and cell mediated antibodies and a series of effector systems involving biochemical and cellular mediators. It was recognized that protective, beneficial effects, as well as tissue damage, could result in functioning of recognition and effector system. As yet, there is little direct information relating to the relative importance of the immune phenomena in beneficial effects as contrasted to destructive effects in periodontal disease. Questions regarding the role of immune processes in periodontal disease were discussed. Those considered meaningful are presented in functional outline below:

Recognition Systems

Antibodies

Q. What are the specificities of antibodies found in the gingival tissues?

Q. What is the severity of periodontal disease in individuals with antibody and immunoglobulin deficiencies?

Q. What is the effect of antibodies on bacterial dental plaque formation? Does the immune response help or hinder plaque formation?

Cell-mediated

Q. What is the effect of soluble mediators of cellular immunity on collagen?

Q. What is the relationship between the level of cellular immunity to oral bacterial antigens as measured by in vitro assays, of peripheral and gingival lymphocytes, and severity of periodontal disease?

Q. What is the effect of soluble mediators of cellular immunity on bone resorption?

Effector Systems

Biochemical Mediators

Q. What is the severity and form of periodontal disease in individuals with deficiencies in the complement system, especially those deficient in C_2 and C_1 esterase inhibitor?

Q. How do complement levels vary in individuals in whom experimental gingivitis is induced?

Cellular

Q. What is the severity and form of periodontal disease found in individuals with severe leukocyte deficiencies such as in cyclic neutropenia and agranulocytosis, and individuals treated with ALS?

Q. What is the severity and form of periodontal disease in individuals with depressed leukocyte function such as those with depressed neutrophil or monocyte chemotactic ability?

Q. What is the severity and form of periodontal disease in individuals with defects in phagocytosis? (e.g. in chronic granulomatosis disease characterized by inability of neutrophil to kill ingested microorganism.)

Many of the above questions could be studied using one or more of the following types of subjects: (1) Individuals with depressed (or augmented) immune recognition or effector systems. (2) Age-matched groups of individuals with widely differing severity of periodontal disease, but who are otherwise "healthy." (3) Healthy individuals in whom experimental gingivitis is induced.

The workshop participants felt that the following diseases which affect recognition or effector functions of the immune systems could be used for intensive study directed at answering one or more of the questions mentioned above:

Acquired Adult Hypogammaglobulinemias
Hodgkin's Disease
Complement Deficiency Diseases
Hereditary Angioneurotic Edema (in which C_1 esterase inhibitor is defective)
Chediak-Higashi Syndrome
Chronic Granulomatous Diseases
Cyclic Neutropenia
Di George Syndrome
Lymphopenic agammaglobulinemias

The general opinion of the workshop participants was that many of the questions posed could be reasonably well studied at the present with existing expertise. However, several areas of inadequate technology and the ever present problems of experimentation on humans should be well thought out before experiments were attempted.

As a result of the possibilities brought out at the workshop, NIDR has initiated efforts to develop coordinated clinical and laboratory studies at several medical centers. These will involve two types of patients: (1) those with known immunologic abnormalities, in whom it will be determined whether their specific defects are associated with susceptibility to periodontal disease; and (2) those without known immune abnormalities, who show severe periodontal disease. The second group will be thoroughly characterized by a battery of immunologic tests to determine whether increased susceptibility to disease is associated with heretofore undetected immune defects.

Staff Document Prepared for Planning Meeting, February 1972. A background draft was prepared by staff to outline and describe periodontal disease targets for the next five to ten years. Used to facilitate discussion at the consultants advisory meeting, this document considered the state of knowledge in a broad way, and presented recommendations of both a general and specific nature. For convenience, periodontal disease was conceptualized as a single basic disease process involving three stages

of development or sets of processes: microbial plaque development on teeth, gingival inflammation, and alveolar bone resorption. In order to increase the probability of developing rational measures to control periodontal plaque formation, it was suggested that research efforts concentrate on fully characterizing the plaque at all stages of its maturation. Important questions to be dealt with included the following: (1) What bacteria are present in plaque? (2) Which are adhesive and what adhesive substances do these bacteria make from what substrates? (3) Is the exact nature of the cementum critical for adhesion? (4) Which bacteria make toxic products and what substrates are required for this activity? (5) What are the contributions of the saliva and gingival crevice fluid to the processes of bacterial growth, mineralization and adherence, and to the synthesis of toxic chemicals and inflammatory substances?

Since studies concerned with the multiple cellular and biochemical events of local inflammation apply directly to the problem of gingivitis, such efforts should continue to be nurtured, and further attempts made to clarify the means by which local tissue structural elements become degraded. Studies of the significance of the several varieties of immune inflammation thought to occur in periodontal disease were encouraged and plans for examining in humans the relationship between specific immune factors and periodontal disease were cited.

Research on the important problem of localized alveolar bone resorption looms as a hurdle to be surmounted only by imaginative efforts. The manner in which mineral is dissolved remains poorly understood, and the exact means by which organic matrix material is removed has not been fully explained. The details of these processes should be thoroughly clarified and their relation to inflammation made plain.

Whereas some aspects of periodontal disease can be studied in humans, many important features of plaque formation, inflammation, and bone resorption can best be studied in the laboratory. Therefore, throughout the draft, great stress was laid on full exploitation of already available *in vitro* and *in vivo* experimental models, and strong exhortations were made to devise new systems with a high degree of disease pertinence.

Planning Meeting in February 1972. Using the document summarized above as a point of departure, an *ad hoc* committee met in February 1972 to discuss plans for the development of research in periodontal disease. During the meeting many thoughtful opinions were expressed, a number of subjects were given detailed consideration, and some highly valuable suggestions were offered, all of which served to heighten awareness and help all of us to understand the nature of the tasks ahead.

The committee's general advice was that the Institute should develop short term plans for applied research to take advantage of empirical means of disease control, while concurrently supporting long range studies on the nature of the disease process, because studies of this type may lead to rational means of disease prevention. Since control of dental plaque formation seems to offer

the most expedient solution to the periodontal disease problem, it was the committee's opinion that first priority should be given to studies of plaque prevention. The group also recognized that studies to understand disease mechanisms would demand continuing attention. In addition, the committee recommended that more scientific workshops be sponsored, and offered a cogent suggestion on research manpower. The major points of the discussion appear in the summary below.

1. Plaque Prevention. The committee's view that the highest priority should be given to research on the prevention of bacterial plaque, was based on the assumption that colonization of teeth by bacteria is the first step in a chain of events which inevitably leads to alveolar bone resorption and the loss of teeth. While it seemed clear to everyone that plaque prevention would prevent marginal gingivitis, it was recognized that the evidence was not conclusive that stopping plaque formation would bring the whole disease process to a halt. Nevertheless, interfering with the bacteria seemed to be the most obvious, and perhaps the fastest, way of obtaining concrete results in improving the health of large populations in a public health manner.

The committee proposed that three types of agents be intensely studied; antibacterial agents to prevent plaque formation; chemical agents intended to remove existing plaque; and substances to interfere with mineralization. Promising antibacterials mentioned were Kanamycin, Vancomycin, and Chlorhexidine. The participants thought that combating the adhesiveness of bacteria is not likely to pay off soon, nor did direct immunization approaches seem too promising at present. At the same time that preventive studies are carried out, support should be provided to conduct coordinated clinical and laboratory studies seeking to understand the biology of the plaque, including its nutrition, metabolism, bacterial and chemical composition, adhesive mechanisms, antigenic nature and pathogenic potential. Studies of serum, saliva, and gingival fluid should be included in such coordinated efforts. Since few existing laboratories or clinical research units are presently capable of carrying out the expanded types of coordinated studies envisioned, it was recommended that centers of excellence be established so that a broad, cohesive program can be developed.

Another suggestion fully in accord with this idea was that the NIDR invest approximately half of its expected special emphasis funds in group research efforts of the program-project type.

2. Disease Mechanisms. It was the committee's opinion that studies on the mechanism of the disease should involve clinical, animal, and laboratory experiments. Projects should consider the natural history of periodontal disease in humans with no other coexisting disorder. Such studies should begin with patients at an early age and should continue for many years in an attempt to clarify the relationships of the pathologic events which take place. These longitudinal studies should show clearly whether chronic gingivitis always leads to alveolar bone destruction and the loosening of teeth in different populations. A second type of study on periodontal disease mechanisms would attempt to discover relationships between periodontal disease

susceptibility and known medical conditions including connective tissue disorders and deficiencies of the immune apparatus. Medical conditions considered fruitful for this kind of investigation included such connective tissue diseases as Ehlers-Danlos syndrome, Raynaud's disease, and Scleroderma, as well as several other conditions of immune impairment such as seen in Hodgkin's disease, cancer chemotherapy, kidney transplantation, and various other hereditary or acquired immune deficiency diseases. There was agreement that these human studies should be supplemented by selected animal experiments. For studies of periodontal disease in otherwise normal patients, it was stated that the potential of beagle dogs and squirrel monkeys as models to mimic the human disease was good. The possibility was raised that the bacteria responsible for periodontal disease might have antigenic determinants similar to those of oral tissues, and it was suggested that this question be examined. Great stress was laid on the need for studies designed to show relationships between the inflammatory process in the gingiva and the destruction of collagen fibers and bone resorption. It was brought out that investigations dealing with those questions would have to depend upon a variety of novel laboratory and animal bioassay systems.

3. Periodontal Disease and General Health. A heretofore neglected area marked by the committee for special attention was the effect of periodontal disease on general health. According to one of the participants, while a great deal of attention has been paid to the oral manifestations of systemic disease; relatively little attention has been paid to the systemic manifestations of oral disease. Although the microorganisms in the periodontal plaque do not seem to invade the body in great numbers, there is evidence that they release products, including soluble antigens with endotoxin activity, and that these penetrate into the oral tissues continually. Studies of local tissues and serum indicate that these antigens have systemic as well as local effects. It is known, for example, that endotoxins influence the general susceptibility of the host to infection by other organisms. Whether such mechanisms might aggravate existing medical disorders or affect the fetuses of pregnant mothers with periodontal disease is not known. Accordingly, full explanation of the total systemic effect on general health should be made.

4. Other Recommendations. One suggestion was that a number of research centers should be established so that comprehensive research projects could be carried out. Another suggestion was that a small group of special investigators be granted awards to devote essentially full time to the study of periodontal disease. These awards might profitably be granted for at least five years to scientists with proven capabilities so that there would be a high probability for research accomplishment. The committee was also in favor of fostering workshops on specific problem areas to review and summarize past progress and to set new directions for future research.

5. Implementation: Present Status. As a result of the many informal and formal discussions among staff and consultants that have taken place over a considerable period during the year, a great deal of support and impetus has been given to our planning efforts. Since these activities have taken a major portion of staff time this year, there has been some delay in program

implementation. Nevertheless, the impact of the various recommendations already seems to have been reflected in several ways.

The strong emphasis on the need for plaque prevention prompted a re-evaluation of plaque prevention programs already being supported by NIDR, as well as an encouragement for the submission of new applications.

Recognizing the international distribution of research competence in periodontal disease, it seems clear that NIDR must look not only to scientists in the United States but also to those abroad.

Research Highlights

In spite of this year's heavy commitment to periodontal disease research, the full measure of its impact will not be realized until an inevitable lag period has elapsed. Nevertheless, certain significant findings can be cited now. Foremost among these was a revealing study emphasizing the importance of bacterial adhesion as a mechanism of virulence in local disease, and a brilliant research endeavor which brought forth evidence to show how salivary immune mechanisms protect the host. Other projects involved the composition and metabolism of periodontal plaque, and possible mechanisms of disease in gingiva and bone; with attention given to both local and systemic factors. Finally, brief descriptions were made of certain experimental animal models which may offer promise.

Plaque

Using a soft replica technique with scanning electron microscope, investigators at Boston University have been able to study sequential changes in developing human plaque. These have generally substantiated earlier morphological studies carried out by other technical means.

At Forsyth Dental Center, continuing studies on the microflora of human supragingival plaque have attempted to quantitate the numbers of bacteria in a developing plaque on a specific tooth site. The results show that early plaque contains large numbers of streptococci. Within 16 days the plaque increased both in microbial number and complexity, but after this period the plaque showed some stability in both of these characteristics. A related study is analyzing, by chematography, the nutritional factors necessary for the growth of Actinomyces naeslundii, an organism common in periodontal disease plaque. At the same time, important studies have been under way, also at Forsyth, on protein composition of supragingival plaque. In this work, the immunoglobulins of plaque collected from 150 individuals were identified and assayed. Significant concentrations of IgG, IgA, and human serum albumin were found in the plaque samples.

In another study related to periodontal plaque formation, a survey was made to determine which oral microorganisms would calcify in a synthetic medium. This work, conducted at the University of Texas, Dental Science Institute, tested fourteen organisms, all isolates from either man or the marmoset.

Examination by a variety of appropriate methods showed that four of the microorganisms calcified. In every instance, the mineralization process started in an intracellular location.

Since bacterial endotoxins in plaque are produced by a number of Gram-nagative organisms, and may be extremely important in the pathogenesis of periodontal disease, a fair amount of attention has been devoted to these agents. At the University of Oregon, investigators have studied the liberation of toxins into the supernate by the parent organisms in an in vitro system. So called free endotoxin was found to be produced during active phases of growth of several species of the indigenous oral microbiota. More than half of the total free or extra-cellular endotoxin ultimately found in the culture supernate was liberated during logarithmic phases of growth. Production of this free endotoxin did not seem primarily to be a consequence of cell lysis. On the other hand, electron microscopic evidence suggested that the mechanism of release involved the formation of small blebs of cell wall material.

In a continuing study at the University of Minnesota, the relationship between the presence of hydrogen sulfide in dental plaque and the degree of gingival inflammation was examined. Preliminary findings showed hydrogen sulfide production in 90 percent of 134 gingival pockets that exceeded 4mm in depth.

Since the topical agent, chlorhexidine, has been used in a number of clinical studies to inhibit the formation of dental plaque, the effect of this topically applied agent upon the metabolism of gingiva is of interest. Investigators at the University of Iowa have shown that repeated chlorhexidine applications caused a marked increase in the activity of two enzymes in the gingival tissue. In this study a concentration of 2 percent chlorhexidine was used daily on the gingiva, and the laboratory results were obtained by microchemical techniques.

In another in vitro study, it was shown that chlorhexidine exerted effects upon the adhesion of epithelial cells. Specifically, when slices of teeth were treated with 2 percent chlorhexidine for five minutes, there was complete inhibition of the adhesion of tissue culture cells to the enamel portion of the preparations, and partial inhibition of adhesion to the dentinal parts. It was also found in related studies that previously attached cells were easier to dislodge after chlorhexidine treatment.

Disease Mechanisms - Local

Two disease-oriented studies of fundamental significance were recently reported by two trainees in Boston (Harvard-Forsyth). Both projects brought new insight to our understanding of bacterial virulence and host-parasite interactions on human mucous membranes. For example, the relationship between the virulence of Streptococcus pyogenes was shown to be related to its ability to adhere, and the capacity to adhere was shown to be related to the known virulence-associated M-protein. Electron microscopic observations showed that this organism attached to epithelial cells by means of a fuzzy surface

coat previously shown to contain the M-protein. Organisms without the M-protein and already known to be avirulent were shown to be incapable of adhering to epithelial cells.

Also elucidated was the apparent role of parotid secretory IgA, it being shown that this immunoglobulin inhibited the adherence of specific oral strains of S. salivarius, S. mitis and S. Sanguis to human cheek epithelial cells. Proper laboratory controls corroborated this data. This study indicates that the parotid IgA inhibits the adherence of specific bacteria to mouth epithelial cells more or less continuously. Through this mechanism it maintains a suppressive effect on bacterial adherence throughout the lining of the mouth and thereby prevents local soft tissue infection. This research achievement is considered to be a brilliant and outstanding contribution to our understanding of the mechanisms of mucous membrane infections.

Studies at the University of Oregon on the role of bacterial products in periodontal disease have involved tests of crude soluble extracts of human dental plaque. These soluble extracts of human plaque have been tested for inflammatory-inducing potential when topically applied to the healthy gingiva of dogs. As a measure of the inflammatory response to this treatment, assays were made of the resulting kinin and kallikrein-esterase activity. The results indicate that saline-soluble products in human plaque may initiate acute gingival inflammation by activating the kallikrein-kinin system.

The chemotactic properties of dental plaque were studied in a project at the University of Minnesota. This study dealt not only with the role of complement in the generation of chemotaxis, but also with plasma and serum factors which affect the phenomenon of leukocyte chemotaxis. It was found that the control antigen-antibody complexes caused chemotaxis in the presence of complement, but did not induce this activity alone. In contrast, dental plaque brought about chemotaxis with and without complement. These findings are confirmatory of the work of others. The most interesting finding of this study was the demonstration that complement-inactivated plasma or serum had an unexpected but consistent inhibitory effect upon the non-complement dependent chemotactic properties of the plaque.

The role of immunological inflammation in the etiology of periodontal disease continues to receive growing attention. The different types of hypersensitivity reactions are gradually being examined as possible mechanisms in the pathogenesis of the disease. In a recent report from the University of Washington at Seattle, investigators described experiments on a type of hypersensitivity that had not been examined before in oral tissues. For the first time the clinical and histologic features of delayed hypersensitivity due to a compound of the dinitrofluorobenzene type was demonstrated. After proper sensitization, animals receiving a topical challenge of this low-molecular weight compound intraorally showed the classical local hypersensitivity reaction, including focal necrosis.

In significant studies attempting to relate immune-induced gingival inflammation to the alveolar bone resorption of periodontal disease, workers at the

State University of New York at Buffalo presented evidence implicating the complement system. This work was begun because present evidence suggests that immune complexes which activate the complement system are actually found in the gingival tissues of patients with chronic periodontal disease. The scientists found that a complement-generated factor caused bone resorption in a bone tissue culture system. No resorption factor was produced when the serum containing the immune complex was heated to destroy complement activity.

In a study at the University of California at San Francisco, prostaglandins have been studied as potential mediators of the bone loss observed in periodontal disease. These fatty substances possess two types of activity which might be important in the disease process. They cause an increase in the vascular permeability and possess potent bone resorptive activity in tissue culture. In this particular study the possibility of bacterial synthesis of prostaglandins by oral organisms was investigated because it was believed bacteria of the plaque might serve as a potential source of the bone-destroying factor in advanced periodontal disease. Extracts from certain oral microorganisms found in dental plaque did indeed show prostaglandin activity in a bone tissue culture system. Control experiments showed that this activity was not due to substances already present in the media in which the bacteria were grown. Further evidence to confirm the presence of the bone resorptive activity from bacterial extracts was obtained when the activity was abolished by specific prostaglandin inhibitor, polyphloreitin phosphate.

In a collaborative study involving Fairleigh-Dickinson University and Columbia University, investigators have examined the levels of sodium, calcium and potassium in the gingival fluid from patients with necrotizing ulcerative gingivitis and in patients with chronic gingivitis and compared these levels with those of patients having nearly normal gingiva. Higher levels of sodium and calcium, and higher sodium to potassium ratios were found in patients with necrotizing ulcerative gingivitis than in the normal patients. Furthermore, the sodium to potassium ratios were significantly higher in the fluid from the necrotizing ulcerative gingiva than in the fluid from the moderate chronic gingivitis fluid. Measurement of these ions and of the sodium-potassium ratio, according to these investigators, may provide an objective means of assessing the severity of gingivitis.

Disease Mechanisms - Systemic

The chemical conversion of the hormone progesterone was studied in both normal and chronically diseased gingiva by investigators at the University of Missouri at Kansas City. The results obtained from eight separate experiments indicate that diseased gingiva is more efficient in metabolizing progesterone than is healthy gym tissue. The addition of pyridine nucleotides to the *in vitro* incubation system seems to enhance the capability of specimens of the diseased gingiva to metabolize progesterone. The results were confirmed by identifying and quantifying the metabolites.

In a study aimed at explaining the gingival hyperplasia caused by diphenylhydantoin at the American Dental Association Research Institute, workers have

developed methods which promise to explain the mechanism of this drug action. According to these investigators it is now possible to make a simultaneous gas-liquid chromatographic determination of diphenylhydantoin and its metabolites in biological specimens. Using these methods, the levels of diphynylhadantoin and its major metabolite were examined in patients being treated with dilantin. Assays of samples of serum, saliva and gingiva revealed that levels of the parent drug were highest in serum, intermediate in gingival tissues, and lowest in saliva. In contrast, levels of the metabolite were highest in the gingiva, intermediate in serum and lowest in saliva. There was no correlation of dose, severity of hyperplasia, or degree of inflammation with the levels of parent drug or metabolite in the specimens.

Interesting studies on a mutant mouse with diabetes mellitus similar to that seen in humans have been reported by investigators at Boston University. These workers made studies of the tissue glucose and glycogen levels in the mutant mice and compared them with control animals. Although there was no relationship between the tissue glucose and blood glucose and no specific vascular changes, it was possible to correlate the severity of gingival inflammation with age and tissue glucose levels.

A clinical study of the effect of sex steroid treatment on 15 menopausal patients with desquamative gingival stomatitis was conducted at Baylor College of Dentistry. Both systemic and local hormone treatment was evaluated, as well as local hygiene procedures. Beneficial results were uniformly demonstrated by clinical and histologic assay after three to twelve months of treatment.

Another study at Baylor College of Dentistry sought to establish the relationship between chronic diffuse gingival stomatitis in women and altered immune response. Significant elevations of immunoglobulins were noted in many instances. These changes correlated well with the degree of inflammation seen in the gingival biopsies. After hormone therapy with estrogen and progesterone the elevated immunoglobulin G levels returned to normal.

Animal Models

In the evaluation of therapeutic procedures in periodontology, progress has been limited by the lack of an animal model system in which the clinical, radiographic and histopathologic picture of periodontal disease mirrors that are seen in man. Experimental pathologists at the Eastman Dental Center have found a way to develop in Rhesus monkeys a pathologic pocket which appears to be identical to those which develop in man after many years of chronic disease. The investigators produced these irreversible lesions by placing orthodontic bands around the necks of the teeth for approximately three months.

Studies conducted by investigators at the American Dental Association Research Institute have sought to explore the chimpanzee as a suitable experimental animal for periodontal disease experimentation. The results so far indicate that these animals have periodontal disease quite similar to the human disease.

In continuing his studies of the fibers which hold teeth to bone, an investigator at the University of Tennessee has added new evidence from primate studies to support his previous findings in the mouse. A previous annual report described this worker's findings that certain fibers passed from tooth through the alveolar bone to the adjacent tooth in rodents. Thorough serial section studies have now been made in the marmoset, and it has been found that this primate also shows uninterrupted fibers passing from the periodontal ligament through the entire thickness of the surrounding alveolus. Orientation, distribution, and attachment of these unique fibers were examined in detail and the implication of these findings as they may relate to periodontal disease or orthodontic treatment were discussed. It was claimed that the findings indicate an interdependence of teeth not previously recognized.

DEVELOPMENTAL BIOLOGY AND ORAL-FACIAL ANOMALIES PROGRAM

In accord with its multifaceted program goals, the Developmental Biology and Oral-Facial Anomalies Program seeks to advance current scientific knowledge along a broad front of biomedical research concerned with the normal and abnormal structure and function of the oral-facial region.

Several workshops and conferences were held during the year so as to provide staff with the most authoritative analyses of promising research areas for program planning purposes as well as to benefit the scientific community at large. Research goals were advanced by means of research grants, interdisciplinary program projects, training grants, fellowships and career development awards.

State-of-the-Art Publications

The proceedings of a conference on genetics, bone biology, and analysis of growth data, supported by the Developmental Biology and Oral-Facial Anomalies Program, were published by Pergamon Press under the title "Cranio-facial Growth in Man." The text was edited by Robert E. Moyers and Wilton M. Krogman.

Workshops and Conferences

1. State-of-the-Art workshop, "Cleft Palate: Clinical Research," contracted to the American Speech and Hearing Association (NIH-71,643).

A series of workshops under this contracted program covered a variety of disciplines relevant to cleft palate research: surgery, speech, language, and psychology; dentistry and orthodontics; developmental biology and etiology; otolaryngology; and pediatrics. These were followed by two interdisciplinary meetings attended by several representatives from each of the initial workshops. The workshops resulted in a thorough and authoritative assessment of current trends and accomplishments as well as in an identification of promising areas for future research endeavor. Proceedings from the individual workshops will be published in appropriate journals; a joint publication is also anticipated.

2. State-of-the-Art Workshop, "Description of Occlusion," November 22-23, 1971, Bethesda, Maryland.

Fourteen participants were in attendance, representing both basic and applied areas of science. Among the highlights of the workshop were: (a) recognition of serious shortcomings in a number of philosophies concerned with occlusion due to lack of a sound scientific base; (b) methodologies of basic physiology to be adapted for studies of function, and adaptational properties of specific muscles comprising the oral-masticatory system; and (c) emergence

of quantifiable methodology in terms of electronic monitoring of positional changes of the mandible for better characterization of normal and abnormal temporo-mandibular joint function. A manuscript of workshop proceedings is currently in preparation.

3. Workshop on "Training of Clinical Researchers in the Region of the Head and Neck" November 29-30, 1971, Bethesda, Maryland

Seventeen participants were in attendance including a dental dean and specialists in general surgery, head and neck surgery, oral surgery, ophthalmology, otolaryngology, and plastic surgery. Discussion centered on the current fragmentation of this anatomical region through clinical specializations. Highlighted among the pressing and numerous needs were: (a) promotion of post-graduate fellowship programs in the area of head and neck health sciences in order to strengthen research capabilities of the numerous specialists concerned with this area of research; (b) development of new post-doctoral training programs for professionals intent upon future research careers; and (c) development of models for combined degrees as basic preparation toward research careers in the area of head and neck.

4. Annual Conference, "Orofacial Anomalies: Clinical and Research Implications,: under training grant to the Joint Committee on Dentistry and Speech Pathology-Audiology (DE 210), Phoenix, Arizona. April 15-17, 1972.

The conference focussed on congenital and acquired malformations other than cleft lip/palate. Highlighted among congenital anomalies were otocephalic malformations, craniofacial synostoses, and selected inherited syndromes associated with deafness and craniofacial malformations. Ablative surgery was the main topic with regard to acquired malformations. Proceedings of the conference will be published by the American Speech and Hearing Association.

Programming Visit for PL 480 Funds

Numerous programming visits were made by staff during FY 1972. Most extensive among these was a trip to Yugoslavia, August 24-September 11, 1971. Its purpose was to contact investigators who are engaged in research relevant to oral-facial anomalies, particularly cleft lip and palate, in order to generate interest in submitting applications for PL 480 money.

Key researchers were identified from recent Yugoslav publications and through personal contacts prior to the visit. Most of the professional expertise was found centered in Belgrade, Zagreb, and Ljubljana. The following institutions were visited: In Belgrade (1) The Stomatological Faculty, University of Belgrade, and (2) The Military Medical Academy; in Zagreb (1) The Faculty of Stomatology, University of Zagreb, (2) The "Andrija Stampar" School of Public Health, and (3) The Institute for Maxillofacial Surgery, University of Zagreb; in Ljubljana (1) The Department of Maxillofacial Surgery, University of Ljubljana, (2) The Institute for Pathological Morphology, (3) The Department of Plastic Reconstructive Surgery, University of Ljubljana, and (4) the Medical Faculty Clinics. In all, over 40 investigators were contacted.

Discussions centered around NIDR program interests, NIH review procedures, additional requirements relevant to PL 480 applications, local conditions at Yugoslav institutions of higher learning, as well as the role NIDR program staff could play in order to facilitate the processing of applications. Although Yugoslav faculty were found to be overburdened with teaching and patient care, most were nonetheless enthusiastic about expanding their activities into the area of research. Many have excellent research training acquired outside of the country. Similarly, much of the Yugoslav case material might be difficult to find elsewhere and some of it was noted to be entirely unique. With regard to craniofacial anomalies, a number of population isolates are yet completely unexplored.

Research Highlights

Progress was made in areas of cleft lip/palate, malocclusion, developmental biology, speech, and oral sensation and perception.

Cleft Lip/Palate

Investigation into the causes of clefts in order to prevent their development follow two paths. In the first instance, it is hoped that statistical analyses of human epidemiologic surveys, coupled with studies of families where several members are deformed, will permit determination of various types of clefts as well as a distinction between their hereditary and environmental causes. Secondly, human and animal embryological specimens are studied in an attempt to elucidate the process of fusion of the palatal shelves as well to determine the mode of action of potential terotogenic agents such as vitamins, hormones, tranquilizers, and others.

Recent reports with regard to incidence of clefting are available as a result of a number of studies of select populations such as those in Denmark, Hawaii, and Iceland. The work is being conducted by several groups of investigators, most notably at the Universities of Indiana, Hawaii, and Alabama. Incidence of CL/P is one in every 700 live births in the general Danish population. The risk to a CL/P Dane of having a CL/P child is 3 percent, whereas with CP it is twice as great. The incidence of clefting (CL/P) is one in every 398 births in Iceland. These results are based on complete coverage of all births between 1954 and 1966, including still births. CL/P is four times as common in families with CL/P as in the general population. It appears most frequently in parents and siblings rather than in uncles, aunts, and cousins. CP is eight times as common among relatives as in the general population.

Grouping, heredity, and treatment of a broad spectrum of facial disorders are being investigated at the Hospital for Sick Children in Toronto, The Center for Craniofacial Anomalies in Chicago, The University of Minnesota, and at other centers. Investigators at Minnesota identified a number of syndromes, many of which are hereditary. According to these researchers, clefts are a part of 65 syndromes. Of these, 16 are believed to be non-genetic, 15 a result of visibly abnormal chromosomes, 4 due to inherited sex-linked traits, and the

remainder resulting from autosomally inherited (dominant and recessive) traits.

Additional progress has been achieved in several areas concerned with the mechanisms of palatal shelf movement. Among other possibilities, an adequate blood supply in the mouth and palate might account for the shelf force that enables them to turn to a horizontal position prior to fusion. Research conducted at the University of Michigan reveals a dissimilar distribution of blood vessels in embryonic mouths and palates of control and experimental mice with clefts caused by cortisone. The vascular plexus of cleft embryos follows a more primitive pattern. It fails to evolve into a normal symmetrical plexus typical of their normal counterparts.

Involvement of the tongue and active fetal head motion as a basis for turning of the palatal shelves continues to be investigated at the University of Texas, Galveston. Administration of tranquilizers, muscle relaxants, and anti-inflammatory drugs to rodents will produce a number of cleft offspring. As a further step, fetal tongues will contract upon electrical stimulation, yet clearly developed muscular tissue does not appear until after palatal closure.

Glucose and insulin effects on energy reactions in cultured palatal tissues are being studied at the University of Minnesota. Results indicate an early energy loss in cells identified as "programmed to die." Reports from Brussels pertain to rat palatal shelves cultured in an oxidizing agent so as to change their energy supply. As a result, fusion of the ectoderm proceeds normally, yet the mesenchyme shows numerous signs of damage.

To gain better insight as to treatment of incompetent palates, a series of pharyngeal flap operations were investigated at the Eastman Dental Center at Rochester. The findings indicate the following factors most often responsible for failure: operations were performed after the age of 12; the patients had either an immobile palate, or an exaggerated nasopharyngeal depth, or too wide a velopharyngeal gap; the flap was inserted too low at the pharyngeal end.

An attempt to avoid surgery, yet to improve speech by training patients to move their pharyngeal muscles voluntarily, has proved ineffective both at the University of Kansas and Stanford University. The patients can learn voluntary motion in isolated utterances, but not during ordinary speech. Scientists at Duke University report the successful use of palatal speech stimulators to reduce the velopharyngeal gap during sustained phonation. According to findings from the Eastman Dental Center, surgery decreases muscle mobility, yet will facilitate speech if it narrows the throat gap to a manageable size. Studies at the University of Arizona involve an effort to relate articulation abilities with response to treatments to modify movement of posterior pharyngeal wall and palatopharyngeal closure. The base-line and treatment changes are being related to measurements of oral form recognition.

A close correlation between oral air pressure and articulation tests in terms of predicting success of speech therapy was noted by investigators at the University of Iowa. It would be frustrating, expensive, and harmful to attempt therapy in children who lack the basic potential for speech. Investigators from the University of Kansas report that scores of their sound production tasks suggest very early the outcome of therapy and will enable the therapist to decide very quickly whether or not to continue with the training.

Speech scientists at the University of Washington, Seattle, are studying such specific jaw functional activities as jaw acceleration, jaw velocity, and jaw displacements as initiated through speech and audio stimulation. They are incorporating the methodologies of electronic transducers and selective anesthesia of nerve fibers, including alpha and gamma components, to answer questions of motor control in speech. There seems to be general agreement that the degree of palatal elevation demonstrated by patients is related to sensory information about palatal location available to the patient.

Since most cleft children have ear infections and some hearing problems, investigators at the Dental Research Center at Chapel Hill, North Carolina, made a survey of microorganisms in the naso and oropharynx of normal and cleft palate children. The same varieties of organisms in roughly the same proportions appeared in both, yet cleft children recovered more slowly and often suffered from chronic residual infections. The reasons for hearing problems were investigated at the University of Pittsburgh. It was demonstrated, by instilling a radioopaque fluid into the eustachian tubes of normal and cleft infants, that normally both ends of the tube open during swallowing. In cleft children only the ear end of the tube will do so. Fluid will therefore accumulate in the middle ear. Investigation of the fluid indicates that is is usually very viscous, contains little glucose, but has extremely high levels of various active enzymes as well as a number of inflammatory cells.

Additional evidence is now available from the University of Iowa that cleft palate patients seem to have slightly lower intelligence quotients than those with cleft lip and palate regardless of hearing ability. Psychosocial research concerned with the effects of clefts on the patient, parents, and their environment is undoubtedly an extremely difficult area of investigation. Painstaking work is being conducted at a number of cleft palate centers.

Malocclusion

1. Epidemiology: A basic step in the investigation of a biological disorder is to define the occurrence and variation within the population. In the variability of statural growth, investigators in Australia have found that the adolescent growth curves of Central Australia Aborigines are generally similar to the growth curves of British children. While Aborigine girls were found to mature to about the same final stature as British girls,

Aborigine boys matured to a final stature 1.7 cm. less than their British counterparts. The investigators speculated that malnutrition and illness may be responsible for this difference.

In the variability of occlusion forms, the occlusion of 8,188 Hawaiian children was examined by investigators from the University of Hawaii. They found that Caucasians had a higher frequency of "ideal" occlusion and that relative to Caucasians, Oriental (Chinese, Japanese, and Korean) children had a higher risk of mandibular protrusion, crowded teeth, malalignment of teeth, and frequency of congenitally missing teeth. Filipinos had posterior occlusion comparable to Caucasians but less overbite and more malalighment. Children of Hawaiian parentage were intermediate between Caucasians and Orientals in malocclusion. There was no significant effect of hybridity of children, indicating that human racial crosses represent no additional risks in malocclusion.

Also at the University of Hawaii, the theory of compensatory interaction between developing teeth of the same type was tested by studying tooth size in unilateral absence of a maxillary lateral incisor. The expectation is that the other teeth present on the affected side will be larger than their counterparts on the normal side. The results of this test indicated that when a lateral incisor was missing on one side, the central incisor adjacent to the missing tooth was larger than the central on the other side.

Researchers at Meharry University have compared mean sizes of coronal width of the teeth of several ethnic groups. They found that the teeth of Black Americans were of similar size to those of the Japanese. Black American teeth were generally larger than those of White Americans, Swedish, and English samples; the Black American tooth size was found to be less than the Australian Aborigine and Liberian Negro populations.

2. Treatment oriented research: Studies are being carried out to explore new forms of treatment and to determine the mechanisms responsible for making current procedures successful.

Removable appliances were used to treat 120 children with class II malocclusion at the University of California. After seven years of study it was determined that the treatment produced an increase in mandibular alveolar height in the molar region, an increase in lower facial height, and a reduction of forward growth of the entire maxilla. The growth in length of the mandible did not appear to be significantly influenced by treatment. The activator treatment corrected the mal-relationship of the dental arches but did not correct other aspects of the malocclusion. These findings were confirmed on controlled studies of 36 rhesus monkeys.

Surgical correction of malocclusion is becoming a widely accepted treatment procedure. Thus, it is important to document the effects of radical and sudden change of oral-facial components upon the future functional capacity and long range stability of the skeleton and dentition. At the University of Kentucky, studies of cases of mandibular osteotomy indicate that the surgery

prompts changes in tongue posture as indicated by the hyoid position which are apparently related to reflex maintenance of a patent airway. It may be that stability of the surgical result is related to a stabilization of the tongue in a new posture post-surgically. Studies also indicate that in most mandibular osteotomy corrections, the total facial height remains at or near the pre-surgical dimension.

3. Function of Jaws: A considerable portion of the foundation of knowledge of oral-facial tissues centers on anatomical description. Current efforts are being expanded to involve quantitative description of mandibular function. Detailed recordings of incisor and condylar motion are being studied at Case Western Reserve University. Analysis of data has revealed that the paths of motion of the condyles are quite similar for subjects with "normal" occlusions and malocclusions. This is in contrast to the paths of motion of the central incisor where differences among subjects with "normal" and malocclusion are easily detected. Of interest is the observation that the central incisor remains motionless at closure for more subjects with "normal" occlusion than for subjects with malocclusion. It was also observed in normal subjects that, during function, unexpected contact of teeth with a hard object did not produce a reflex opening of the mandible as previously believed; but there was instead a reflex stoppage of all mandibular movement.

In addition to the above human functional studies, investigators at Harvard University are doing comparative mammalian studies. They hypothesize that all mammals, whether they be insectivores, herbivores, omnivores, or carnivores, show a fundamental similarity in the time and direction of the strokes of the chewing cycle. They have observed that in the insectivorous, omnivorous, and herbivorous forms, the temporomandibular joint plays an insignificant role in controlling or directing the pattern of movement of the lower jaw during the masticatory cycle. It is also suggested that very slight changes in direction of jaw movement and relative masses of the respective parts of the jaw musculature can have profound effects upon the architecture of the skull, topography of teeth, and feeding behavior.

At the University of California, Los Angeles, basic research is being carried out to determine neurological mechanisms which serve to control the function of the masseter muscles of both man and animals. This work has shown that synchronous stimulation of mechanoreceptors in the tongue evokes a complex, triphasic pattern of response. It is known that painful stimulation of the tongue inhibits masseter muscle activity; this is thought to be a protective oral reflex mechanism. Stimulation of afferent fibers from mechanoreceptors in the tongue results in two separate inhibitory responses, as well as excitatory response in masseter motor neurons. The bilateral symmetry of response is important for normal coordination of activity between muscles of both sides.

Developmental Biology

To understand the mechanisms operating in malformations or disabilities of the oral-facial tissues it is necessary to conduct basic biological investigations which provide knowledge of the mechanisms of growth and development.

Various studies are currently devoted to bone physiology. At the Medical College of Georgia, thorotrast was released into tibial marrow cavities and into tibial nutrient arteries. The label indicated that the general tissue fluid drainage of the tibia is affected in the perivascular connective tissue of Volkmann's canals from the marrow cavity to the periosteal lymphatic vessels. The tissue fluid flow appears to pass from the Haversian vessels through the canalicular-lacunar complex to the peripheral lacunae of the osteone.

Research at the University of Washington resulted in a "mechanochemical hypothesis" for bone remodeling which is induced by mechanical stress. Local bone remodeling is of considerable physiological importance in normal growth processes and in orthopedic and orthodontic therapy. In this study, a model system was designed to stress hydroxyapatite crystals in bone. This in turn altered the solubility of the crystals which provided the required negative feedback message to the bone cells in the form of mechanically induced chemical change and bone remodeling. Special investigative effort is being made to determine the mechanisms of odontogenesis. At the University of Southern California, investigators are studying the epithelial and mesenchymal interactions in tooth development. They have isolated tooth germs from rabbit embryos and have separated the two germ cell-types. Neither cell-type could differentiate in culture independent of the other cell-type but they did become specialized cells when grown together with the noncellular matrix. The scientists have isolated vesicles, some of which contain RNA. This RNA, which appears to be transported between epithelial and mesynchymal cells, may be the messenger mechanism responsible for cell differentiation in odontogenesis.

Nerve conduction in human teeth is being studied at the University of Michigan. Specifically, the mode of conduction of neural impulses through dentin and the mechanism of reparative dentin formation are under investigation. Early evidence indicates that when the inferior alveolar nerve is resected the involved teeth form abnormal dentin. Further, if these teeth are stimulated by cavity preparation, an excessive amount of dentin forms in the pulpal tissue. Also, these denervated teeth show both altered neural endings and odontoblastic changes in ultrastructural analysis.

BIOMATERIALS PROGRAM

The primary focus for research in biomaterials is in the Biomaterials Program area of the Extramural Programs of the National Institute of Dental Research. This activity is chiefly concerned with the materials and methods to restore lost oral tissues or to prevent the degradation of these oral tissues. Thus, by utilizing both grants and contracts mechanisms of support, research is directed toward the development of new and improved materials for preventive, restorative, prosthetic and implant dentistry.

This past year technical assistance in clinical research has been given to the Pan American Health Organization for clinical studies in pit and fissure sealants in Kingston, Jamaica; Lima, Peru; Medellin, Colombia; Bogota, Colombia; and Mexico City. Technical assistance has also been given to Bio-Research Associates in Milwaukee, Wisconsin, and to the West Palm Beach County Health Department, Palm Beach, Florida.

Clinical research has also been stimulated by an interagency agreement with Dr. Joseph Moffa of the Federal Health Programs Services, United States Public Health Service Hospital, San Francisco, California. This agreement has enabled Dr. Moffa to train dentists and non-dentists (auxiliary personnel) to carry out clinical examinations in the restorative dentistry field using established criteria as recommended by the Council on Materials and Devices of the American Dental Association.

The chief of the Biomaterials Program in December of this fiscal year held an ad hoc meeting with Dr. Ralph Phillips, Assistant Dean for Research and Research Professor of Dental Materials, Indiana University; Dr. Gunnar Ryge, Assistant Director for Training, Dental Health Center, San Francisco, California; and Dr. George W. Ferguson, Professor and Chairman of Operative Dentistry, Department of Operative Dentistry and Endodontics, State University of New York at Buffalo to discuss a long range plan of action for the Biomaterials Program. The committee felt strongly that an advisory group should be constituted for the Biomaterials Program. The committee further advised that research in adhesion and adhesive coatings should continue to receive strong support, with particular emphasis on pit and fissure sealant and collagen adhesion. On the other hand, the committee suggested that further research on amalgam would be unlikely to show sufficient improvement in properties. The committee's strongest recommendation was on behalf of clinical research, and the benefits that would derive from conducting a symposium on "Clinical Evaluation Methodology for Dental Materials." Other workshops were recommended to cover the subjects of dental implants(in cooperation with the American Dental Association Council on Dental Materials and Devices); and biocompatibility to develop a mechanism for the establishment and implementation of standard practices and facilities for biocompatibility screening.

In summary, the target areas identified by the committee for the Biomaterials Program are: (a) Biocompatibility, (b) Adhesion and Composites, (c) Implants, (d) Somatoprosthetic Materials, and (e) Technique Simplification.

Some noteworthy accomplishments of grantees are as follows:

Metallurgy

An American Dental Association investigator at the National Bureau of Standards is carrying out a basic study of the constitution diagrams of several binary alloy systems about which there is almost no information. Six noble metals of the platinum family plus six metals of the vanadium family were selected because they are most likely to combine the desirable properties of strength and rigidity while at the same time offering the necessary corrosion resistance needed for alloys that are to be used in dental and surgical procedures. The vanadium-ruthenium system was found to contain only the two terminal solid solutions and no intermediate phases. A tetragonal distortion of the ordered body system occurs as the composition approaches the solubility limit at a little over the 50 percent atomic percentage of ruthenium, thereby giving rise to sharp changes in certain physical properties that should be further studied. These changes are suggestive of possible transformations similar to those which occur in connection with the "memory effect" which was discovered several years ago in the nickel-titanium system. Biomedical engineers and surgeons foresee interesting applications of such an alloy.

Another investigator at the University of Michigan, School of Dentistry has done pioneering research with the chromium-cobalt alloys. By treating such alloys with carbide, a marked increase in physical strength was established, with a corresponding increase in ductility. In addition, the property of high elongation was obtained without sacrificing several other desirable properties required for dental uses.

At the University of Southern California, School of Dentistry, a researcher is studying the long and short rate of ion diffusion from metallic and other dental materials into adjacent hard and soft tissues using the electron microprobe, scanning electron microscope and x-ray spectrometer. He has observed in preliminary short term studies on dogs that cobalt and chromium diffuse from vitallium dental implants into adjacent bone. In another study he has observed that Zn, Mg, F, and Al ions diffuse from zinc phosphate and silicate cements into teeth. Further studies will be made to determine the equilibrium concentration of ions achieved in the hard and soft tissues.

The use of a small amount (1.5%) of stannous fluoride mixed with dental alloy has been proposed recently as a means of reducing recurrent decay at the margins of restorations. Such a material is now available commercially. However, a research team at the University of Virginia, School of Engineering, has recently made some important discoveries concerning this modification. Carrying out corrosion studies on spherical dental amalgams (with and without additions of stannous fluoride before trituration), it was found that the fluoride caused an increase in the corrosion rate because of its leaching.

This action leaves a highly developed porous structure with a large effective surface that can be further corroded. This finding strongly indicates that stannous fluoride should not be added to dental amalgams. Other studies further suggested that when the stannous fluoride is added to toothpaste or used for clinical topical application, it has no effect on the corrosion rate of amalgam restorations. On the other hand, sodium fluoride, when used in this test situation, caused spherical amalgam to corrode.

A few years ago one of our grantees at the National Bureau of Standards developed a new amalgam composed of gallium, palladium and tin that had certain laboratory characteristics superior to regular amalgam. However, its high wetting property caused problems in clinical handling that were later resolved by another grantee at the University of Alabama School of Dentistry and reported in last year's annual report. During the last year these investigators inserted 35 restorations in 15 patients ranging in age from 13 to 25 years. Twenty were class I, 8 were class II, and 7 were class V surface cavities. An early symptom following insertion after 24 to 48 hours was a moderate, continuous, unprovoked pain that lasted 1 to 2 days and occurred only in the occlusal and proximo-occlusal surface restorations. Four restorations had to be removed because of persistent pain. At two weeks the remaining class I and II surfaces showed deterioration such as discoloration, elevation from the cavity, corrosion and cracking. At 3 to 4 weeks, 9 teeth had fractured cusps. At this time all the class V restorations were still in good condition. Although at four months these restorations were still intact, by six months they had all deteriorated.

In a limited number of histologic examinations, covering an observation period of 3 days to 2 weeks, evidence of pulpal damage was present.

Cements

Traditional dental cements are not strong enough to fasten orthodontic wires reliably to teeth. Therefore, dentists have had to place unsightly and often uncomfortable bands around each tooth and then attach wires to them to provide the tension necessary to move the teeth into proper position. However, cements are now being marketed which claim to allow dentists to bond small brackets that hold wires directly to teeth. An Indiana University School of Dentistry researcher confirms that one new type of cement, a carboxylate, adheres well to enamel.

Since cements are also used to fasten gold inlays, bridges, crowns, and various types of fillings, they should be non-irritating to the sensitive dental pulp. Unfortunately, traditional zinc phosphate cements are toxic to the pulp when the intervening layer of dentin is thin, so that liners must be used. Comparison of carboxylate cement with the zinc phosphate cements shows that the new cement is much kinder to the pulp, as well as bonding better to enamel. A force sufficient to pry the cemented object loose usually pulls the cement apart but seldom breaks its bond to enamel. In contrast, the same force will break a zinc phosphate cement cleanly away from the enamel.

Bioengineering

An investigator at the University of Michigan, School of Dentistry has developed three dimensional photoeslastic methods for stress analysis studies in dentistry that represents a major contribution for dental researchers as well as engineers involved in experimental stress analysis.

In another study, an NIDR postdoctoral fellow at Drexel University's Biomedical Engineering and Science Program, has developed and patented an air driven high frequency oscillating instrument for the movement and extraction of teeth. About 8 inches long and somewhat thicker than the pencil-like air drill now used by dentists, the instrument is light in weight and permits a good field of visibility. After attaching the instrument to a tooth by means of a retainer, it is possible to rotate the tooth horizontally through an arc of about 10 degrees around its vertical axis at about 275 cycles per second.

Preliminary work with this instrument was done on fresh human cadavers, monkeys, and dogs. In dogs the required time for removal of a tooth after attaching the retainer was about 10 percent of the time taken when using the conventional hand forceps on the contralateral tooth. Data so far show that any tooth root which can be firmly grasped by the retainer can be extracted without fracturing. The instrument can also be used to realign teeth in a few seconds with minimal trauma. No preoperative separation of gingiva from the neck of the tooth is required. Indeed, the margin of the gingiva around the neck of a tooth removed by this technique is sharply severed, as if by a knife with no tearing of tissue. Postoperative bleeding is less than with ordinary hand forceps, and there is no observable injury to adjacent teeth or jaw during the extraction procedure. The root of the tooth comes out of the socket completely clean with no trace of periodontal membrane attached to it, whereas teeth removed by the hand forceps generally retain traces of periodontal membrane. Finally, there was substantially less alveolar bone disturbance with the new instrument than with the hand forceps as noted by x-ray examination.

Many teeth in the human mouth have visible cracks which may be the result of thermal stresses. Investigators at the University of Utah observed that sudden expansion from heat or contraction from cooling can crack teeth because enamel and dentin expand at different rates. Studying bovine and human teeth with and without amalgam restorations, exposed to thermal cycling between temperatures of 90 degrees F and 140 degrees F, it was found that cracks develop after a few thousand cycles of thermal exposure with temperature differences commonly experienced in the mouth. Studies, using finite stress analysis, are continuing on teeth exposed to temperatures ranging from 35 to 90 degrees F. Tensile stresses in excess of 2000 psi. have been observed in enamel when the ambient temperature is changed 50 degrees F. Thermal stresses within a tooth restored with amalgam are higher than those in a tooth without any restoration and are more subject to fracture. Research is continuing in this area with particular attention toward improving cavity design and also seeking a restorative material with a coefficient of expansion equal to the tooth when exposed to sudden large temperature changes. The Utah research team believes its evidence indicates that pain due to temperature changes is most

probably due to compression or expansion stresses on the nerve since thermal stresses in a tooth are felt immediately after exposure to a change in the environment when the temperature has not yet changed in the region of the odontoblasts of the dentin.

Implants

Interest in implantology has greatly increased in the last few years. Since most of the work has been done in humans there is very little histology or analysis of reasons for success or failure. The approximate life time for many of these implants at the present time is considered to be between 3 and 5 years. It is very important to dentistry that there be a thorough study of the kinds of materials used, the shapes of the implants, the methods of implantation, and a complete scientific follow-up. There also is critical need for information on metals and ceramics with different designs and pore sizes with and without stress.

One ongoing research contract on this subject has been supported for the last year and two other research projects were started recently. Battelle Northwest has initiated a dental anchor implant study using four materials; titanium void metal composite, titanium powder composite, alumina porcelain, and magnesium aluminate spinel. During the past year it was found that titanium was too weak in design, and that a commercial, biocompatible, titanium-aluminum-vanadium alloy is much stronger. Similarly, the ceramic, alumina porcelain was also found to be too weak and its composition was accordingly changed to provide greater strength.

Related research has been focused on anchor design and methods of implantation of twenty-four dental anchors and pins placed in four minature swine; almost all showed postoperative infection and loose fit within a period of four to twelve weeks. In contrast, when splints were used, there was longer retention with practically no inflammation. Better retention also was noted when pins were force fitted.

Two other new research projects on dental implants have been started recently. One is studying specially designed anchors made of very fine sintered vitalium wires, and the other is studying endosseous metal blade implants.

Marine Adhesives

The Franklin Institute Research Laboratories and Battelle Columbus Laboratories have developed methods for obtaining enough cementitious secretions from barnacles and mussels for laboratory studies. Since studies, to date, indicate that the mussel secretes far more material than does the barnacle, most emphasis is being given to this approach. A finding of particular significance is the identification of a protein of over 30,000 M.W. as the chief ingredient of the cement. Very little liquid is present.

The Battelle group found a considerable amount of polysaccharide in the M. Edulis on a seasonal basis, as yet unexplained. It has also developed a technique for drawing mussel foot secretion, before setting, into a small

capillary tube moistened with NaCn to inhibit the setting enzyme, polyphenol oxidase.

The Franklin Institute researchers noted that it is unlikely that a single solvent can be found that will dissolve the arca zebra byssus without degradation. The present approach is to use two solvents, an acid and alkali, performic acid and 5 percent NaOH respectively. These solutions will be used for analysis in the Beckman Protein Sequencer to identify peptide components and then, hopefully, piece together the protein structure of the cement. Thin layer chromatography also is being used as an aid in identifying the peptides.

Significant, too, has been the success of the Franklin Institute group in inducing the arca zebra mussel to secrete its byssus on extracted teeth kept in an aquarium. Fourteen such specimens with attached byssus have now been kept in a rotating saliva chamber at 37 degrees C. for 3 to 16 months. Microscopic examinations have shown no visible deterioration other than darkening. Although the previously reported tensile strength of arca zebra byssus was reported to be of 3000 psi., more recent findings show that the byssus cannot be fractured at 25,000 psi. provided it contains at least 37 percent or more moisture.

Both Franklin Institute and the Battelle Laboratories are continuing their biologic and histologic studies to help elucidate the secretion mechanism and composition of the cementitious protein of mussels. For the coming year heavy emphasis will be placed on the characterization of the protein and its synthesis.

Resin Systems

An investigator from the American Dental Association working at the National Bureau of Standards is conducting a feasibility study of the use of metal powders as reinforcement materials for composite resins. Powders of aluminum, zirconium, tantalum and gold treated with an appropriate coupling agent such as organofunctional silane show prospects of being superior to glass or quartz. Strength and other properties were also improved over metal powders not treated with a coupling agent. Preliminary observations of metal filled resins, burnished on their surface with a steel instrument and viewed with the aid of the scanning electron microscope indicate that the malleability of certain metal reinforcing fillers may result in composites with greater resistance to wear and attrition than the present glass filled composites. Materials of this type may find use in posterior teeth containing incipient carious lesions when used in resins for sealing pits and fissures.

Another researcher at Emory University, School of Dentistry, is conducting long term studies of composites and amalgam which, after one year of observation, show marginal deficiences in class I amalgam restorations, but no such changes with composites. After one and one-half years, class II amalgam restorations were found to be better in anatomic form than the composite, whereas current caries and marginal adaptation were similar for both products. The composite, on the other hand, showed better marginal adaptation than did

amalgam. In a laboratory bruxing test over the same period of time, the composite abraded more rapidly than amalgam while the latter showed a tendency for marginal fracture and proximal flow.

This type of testing is essential before accepting the current composites as a replacement restorative material for amalgam or other alloys.

In another study of class III and V composites and silicates, the former restorative material was found to be superior in both marginal adaptation and anatomic form. No significant differences were noted in color match, marginal discoloration, or recurrent caries.

The Eastman Dental Center is making a long term study of the fate of micro-organisms of dental decay in a tooth sealed in with an adhesive sealant. In a preliminary observation at two months, using a broad spectrum anaerobic method, there was noted a 50-fold reduction in the number of microorganisms that can be cultivated. This finding is of special interest in that it raises the possibility of using adhesive sealing for the temporary treatment of rampant tooth decay until more permanent treatment can be provided.

SOFT TISSUE STOMATOLOGY PROGRAM

Research support in the Soft Tissue Stomatology Program is directed toward the following four major areas: Oral Cancer; Oral-Facial Ulcerative Disorders; Salivary Gland Disorders and Saliva Studies; and Dental Pulp Studies. Program emphasis is on the prevention of infections, and diagnosis, treatment and ultimate prevention of neoplastic and other disorders of the oral soft tissues. Both basic and clinical research projects are being supported to ascertain the normal structure and normal life processes of oral tissues. However, a large number of the 36 research projects funded in FY 1972 are directed toward gaining a better understanding of etiology and pathophysiology of soft tissue diseases. In order to maintain a critical mass of well-qualified and highly motivated researchers, a select number of research training programs, postdoctoral fellowships, and career development awards are supported in oral medicine, oral physiology, oral biology, and experimental pathology.

Program Activities

As a public health problem, cancer of the head and neck ranks among the ten top causes of death in America. Because oral cancer is one of the categorical responsibilities of the National Institute of Dental Research, the program staff undertook a survey to determine the need for research support in this area. The findings indicate that relatively few grants were made either by NIH or other federal agencies in direct support of oral cancer during the five-year period 1965 to 1970. A series of staff recommendations were drawn up and the survey was submitted to the Director of NIDR for his consideration.

An initial exploratory meeting between the National Cancer Institute and NIDR took place in November 1971 to determine areas of mutual interest. A second meeting held in February 1972 resulted in an agreement to establish a cooperative effort between the two institutes concerning the support for oral cancer programs. Staff members of NCI will work closely with the NIDR staff in developing guidelines for the assignment of grant applications in oral cancer to the two institutes, in organizing state-of-the-art workshops, and in studying the feasibility of establishing oral oncogenic research centers in conjunction with existing NCI cancer research centers.

Future Plans

As part of the targeted programs of the 1970s, a major effort is anticipated which will be directed to the development of effective treatment, prevention, and ultimate control of virally induced ulcerations of the lips and mouth. No positive assurance can be made at this time that the additional funds needed to institute a program will be appropriated. However, cooperative efforts between the intramural and extramural NIDR staff are being formulated and a number of two-day workshops to assess present knowledge in the area of soft tissue lesions are being planned. One such workshop, entitled,

"The Treatment and Prevention of Herpes Simplex Virus," will be held at Belmont House, Elkridge, Maryland, on June 15 and 16, 1972. A second workshop directed to the state of knowledge concerning the cytomegaloviruses is under consideration.

Oral Cancer Research

Oral cancer constitutes about 5 percent of all malignant tumors in the United States population. The number of new patients being seen with oral cancer each year appears to be increasing. This is because oral cancer primarily affects people over 40, and there are more Americans in this age range each year. Approximately 60 percent of oral cancers are well advanced by the time of diagnosis, and it has been estimated that as many as 80 percent of all oral cancer deaths could be prevented by earlier recognition of the disease. One of the principal reasons for the delay in recognition of the lesion is that it tends to be asymptomatic for relatively long periods of time.

Studies at the Royal Dental College, Copenhagen, supported by NIDR and reported on in the FY 1971 annual report, employing leukoplakia as a model for detecting and studying malignant transformation of cells are continuing. Recent findings indicate that blood group substances designated as A and B which are present in all normal cells above the basal cell layer of oral mucosa are absent or have a distinctly different distribution in leukoplakia. Positive correlation was found between the degree of atypia and the absence of blood group substances. The demonstration of disappearance of blood group substances in premalignant epithelium may lead to a safer method of predicting malignant transformation of leukoplakia. However, additional studies are needed to confirm these observations.

Also under study at the Royal Dental College is a survey of the incidence of Candida Albicans infection in patients with oral leukoplakia. It has been suggested that some clinical forms of leukoplakia are the result of invasion by the hyphae of this fungus. Findings, to date, indicate that 61 percent of the speckled leukoplakias had a candidal invasion and the same percentage of the speckled leukoplakic lesions showed epithelial atypia, a disorderly maturation of the epithelium. Continued research into the pathogenicity of the organism is in order. Candida Albicans is widely distributed over normal skin and oral mucosa, and primary infections produce moniliasis which clinically appears as white oral lesions that may cover the tongue, lips, gums or buccal mucous membranes. The fungus can become epidemic in a nursery, and secondary invasion of the blood stream may result in endocarditis and, at times, encephalitis.

Studies dealing with the early effects of smoking on surface cytology of the oral mucosa have been supported by NIDR to establish whether or not changes in surface cells occur before the appearance of clinical signs of disturbance. One such study was conducted at the University of Illinois on 37 non-smokers and 41 heavy smokers. Smears were taken from ten clinically

healthy regions of the oral cavity and the papanicoleau technique was used in processing the smears. To identify possible cell changes or differences in cell types, 17 types of cells were recorded, and five shades of cytoplasmic staining were distinguished. A subdivision of cells into three classes, based on nuclear behavior, classifying nuclei as vesicular, pyknotic, or absent, was also made. Using these criteria, a marked cellular difference between heavy smokers (HS) and non-smokers (NS) was observed. The differences were reflected mainly in cell type staining and keratohyaline granule distribution. The proportion of subjects showing these changes was of similar magnitude in some regions but of greatly different magnitude in others. Since only "clinically healthy" regions were included in the study, it can be concluded that an early response to smoking is manifested by a marked shift in incidence of many types of cells. Study of the surface cytology of smokers before they show any clinical signs of change might provide a most useful means for the early identification of particularly sensitive persons.

The same group of scientists is completing a major study of smoking in a Negro population. Preliminary results suggest a higher degree of keratinization and a markedly higher percentage of cells with keratohyaline granules in Negroes than in the mixed population reported above. The study confirms the shift to more immature cells in smokers than was noted in the mixed population. Completed results of this study will be reported in the FY 1973 annual report.

The program staff proposes to direct its future efforts to the general goals as outlined in the FY 1971 annual report. However, collaborative programming efforts in oral cancer by the NIDR in cooperation with the NCI may necessitate a change in priorities and may influence immediate program emphasis.

Oral-Facial Ulcerative Disorders

Oral soft tissue lesions such as herpes simplex and aphthous stomatitis are among the most widespread diseases in the American population. Over 70 percent of those affected experience recurrent episodes which make routine performances, such as eating and drinking, difficult because of painful lip lesions that become hypersensitive to sudden temperature changes. Occurrence in the adult population affects the economy because of absenteeism and concomitant wage loss. The incidence and severity are somewhat higher in children and young adults. Recurrent episodes in these individuals result in loss of time from school and have a greater psychological impact and emotional stress. Despite the widespread distribution of oral soft tissue lesions, clinical diagnosis is still ill-defined; preventive measures are slow in developing; and the causative agents, with the single exception of herpes simplex, have not been established. Present program emphasis centers on the normal cellular events and normal tissue metabolism of oral epithelium. These data are establishing a base line for a better understanding of the nature and pattern of epithelial repair following tissue insult.

In soft tissue diseases, clinical differences are first observed in the altered surface state of the oral epithelium. It is important, therefore,

to understand the factors governing the formation of different surface states (such as hyperkeratinization and parakeratinization). Unlike the synthesis of collagen, knowledge of the formation of keratin in oral epithelium is still sketchy and ill-defined. Yet collagen and keratin constitute the major structural proteins of the oral cavity.

A long term investigation at the University of Washington is attempting to establish a reproducible method of obtaining relatively cell-free fractions from each layer of cornifying epithelium. At the present time, the purity of separation ranges from 95 percent for the upper layers to about 56 percent for the lower cell layers. Additional work is needed to increase the purity of fraction in the lower layers. The separated and suspended epidermal cell fractions will be used for two kinds of studies: (1) to investigate the protein pattern of each layer by using polyacrylamide disc gel electrophoresis; and (2) to perform incorporation experiments to study DNA and protein biosynthesis by using DNA and protein radioactive precursors.

A clear definition of the interrelationship of DNA synthesis and keratinization is needed to provide a base line for a clearer understanding of the pathogenicity of tissues. Such knowledge would afford insights into the nature of the pathology and suggestions for therapy may result. This knowledge is particularly important since hyperkeratinization is often considered to be a premalignant change. Differences in the essential biology of oral epithelium and epidermis are indicated by such facts, for instance, as basal cell carcinoma, which is never found in the mouth; and oral epithelium transplanted over the dermis, which is found to retain its general morphology, whereas epidermis usually undergoes change. The question to be resolved is what factors contribute to the differences in maturation of these tissues and how are they altered in the metaplastic shift from the nonkeratinized to the hyperkeratinized state. From the University of Washington study, it appears that the presence of some mechanism causes the increase of DNA synthesis. Highly suggestive is that the mechanism involves a DNA snythesis stimulant and a DNA synthesis inhibitor. Identification of the presence of such regulators would be of significance for therapeutic approaches to soft tissue disorders. At the University of Illinois, an NIDR-supported group is studying parakeratosis (metaplastic transformation) in oral mucosa using a biochemical approach. Findings show that zinc is an essential element in the animal diet and that a rat on a zinc-deficient diet develops metaplastic changes in the buccal mucosa. Examination of the tissue lesions indicates a shift of acid phosphatase to the periphery of the epithelial cell. The lesion of the cheek is comparable to a cancerous condition, in that circumscribed regions show accelerated production of new cells and accelerated synthetic activity within these cells. Estimates of total synthetic activity in these parakeratotic lesions show the acceleration to be of the order of 20:1 when compared to ad lib fed control animals. These animal studies have an added importance since the data are found to closely parallel clinical patterns observed in certain human pathoses.

Cellular immunity has for some time been thought to play an important role in the host defense to certain oral diseases, particularly to herpes simplex

virus (HSV), vaccinia, cytomegalovirus, and varicellazoster. It is difficult, however, to assess the relative importance of the cellular immune response in vivo. For this reason, several in vitro studies for cellular immunity to viral antigens are being supported by NIDR. One of these investigations has developed and characterized a quantitative, technically simple assay for cellular immunity to HSV antigens, a technique which is also applicable to other viruses. It depends on the fact that lymphocytes are stimulated to enlarge, become metabolically active, and undergo mitosis when they are incubated in vitro with the specific antigen to which they are immune. The proliferative response is measured by the incorporation of radiolabeled precursors into cellular DNA. Application of the assay system to human lymphocytes appears to work so that evaluation of cellular immunity to HSV in humans will be studied during the coming year. A large population of patients with HSV oral lesions is available at the University of Pennsylvania and will be used in the study. This technique could be useful in the case of herpes encephalitis, for which chemotherapeutic agents are available, but which is presently diagnosed by brain biopsy. Delay in diagnosis and the need for this dangerous diagnostic technique will hopefully be obviated by development of a successful, rapid, and accurate diagnostic method.

In view of recent advances in viral immunology and findings pertaining to the structure, chemical composition, and biosynthesis of herpes simplex virus, a major organized research effort to achieve success in the treatment and prevention of herpes simplex virus and other viral diseases of the mouth, has been identified and is incorporated into the NIDR-targeted programs for the 70s. This need was described in the FY 1971 annual report and at that time a number of objectives were outlined. It is hoped that additional funds are made available so that these objectives may be successfully pursued.

Salivary Gland Disorders and Saliva Studies

The microbial ecology of the oral cavity is greatly influenced by the quantity and nature of salivary secretions. Ecological imbalance is brought about when normal salivary gland function is disturbed. Not only is the imbalance manifested in the appearance of various disease states in the oral cavity, such as rampant caries, acute necrotizing gingivitis, xerostomia (seen in the elderly), but there is also disruption of the normal systemic physiological processes, particularly those relating to digestion. In this connection it has been clearly shown that such systemic disturbances as cystic fibrosis can be not only monitored for pathological changes by analyzing the salivary content, but they may also be diagnosed by analyzing the contents of salivary secretions. In addition, analysis of salivary gland development is particularly useful in developing techniques which will lead to early identification of cancers in these sites. Further evidence indicates that the presence of certain immunoglobulins found in saliva contributes to the body's resistance to a number of oral infections such as caries, periodontal disease, and possibly herpetic ulcerative infections.

Since salivary gland functions are important determinants of the ecological status of the oral cavity, a study at the Medical College of Georgia is

attempting to develop an in vitro system in which the production and activity of salivary enzymes can be measured. Submaxillary gland tissue slices are placed in a flow-through chamber and analyzed for enzyme activities (amylase, kallikrein and lysozyme). The results indicate that such a method is useful for measuring the normal rate and kinetics of enzyme release. The same method can be employed to study effects of pharmaceuticals on the glands in terms of changes in rates, kinetics of enzyme activity, and duration of drug response. Future studies will attempt to measure effects of virus (polyoma virus) on the salivary gland in terms of the effects on enzyme activity.

Investigations into the protective mechanisms of saliva by NIDR scientists at the State University of New York at Buffalo, included in the FY 1970 and FY 1971 annual reports, are continuing. Studies conducted during the past year with rabbits involved localizing antibody-forming cells (AFC) of the salivary glands, and identifying the class of immunoglobulin in these cells using combined immunofluorescence with fluorescein-conjugated reagents to detect the antibody, and rhodamine reagents to identify the immunoglobulins. It was found that injection of antigen in saline solution directly into the submandibular gland resulted in the appearance of antibody-forming cells, most of which contained immunoglobulin IgA. However, if the antigen was incorporated in an adjuvant, inflammation was induced in the gland and although antibody-producing cells were found, they were mostly of the IgG or IgM class. It appears at present that local inflammation as well as certain forms of prior sensitization will suppress the IgA cellular response in locally immunized salivary glands. Experiments are in progress with thymectomized rabbits and inbred mice to determine the source of cells which make IgA antibodies in salivary glands, and also to determine the nature of the IgA suppression factor(s) postulated to account for the results.

The same research group is actively investigating the immunological events occurring in mumps (parotitis), using the monkey as a model system. Secretory antibodies to mumps virus in parotid fluid are transient, and detectable levels are present only during parotitis. The Buffalo group feels that there are other factors of resistance which account for the long term immunity seen after mumps infection. Live mumps virus (strain ABC) was inoculated into the parotid gland of monkeys. The monkeys shed virus into their saliva for 6-7 days, and serum neutralizing antibody was detected 1-2 weeks after inoculation. At one week, over half of the gland showed a marked monocytic infiltrate. There was a 20-fold increase over normal IgG cells; a 10-fold increase in IgA cells; and a 5-fold increase in IgM and IgE cells. At three weeks, resolution was evident, with only 10 percent of the parotid tissue area composed of non-epithelial elements. Reinoculation at three weeks failed to induce reinfection; however, at 48 hours after attempted reinfection, a marked monocytic infiltration comprising about half of the parotid tissue had occurred. Most of the cells were nonimmunoglobulin-containing and resembled lymphocytes. It has recently been shown that the infected parotid glands produce interferon and macrophage inhibition factor (MIF). These results show that a local immunoglobulin response, involving IgG, IgM and IgE cells, along with IgA cells, as well as cellular immunity and interferon, plays a role in mumps virus infection. Experiments are in

progress to characterize further the MIF, neutralizing antibodies, interferon, and to look for systemic transfer cell-mediated hypersensitivity in the infected monkeys.

Future research objectives in salivary gland disorders and saliva studies will continue to reflect the types of programs that are presently supported. However, anticipated support for targeted programs would include several areas of overlap of immediate public health interest in this area. They are as follows:

1. Research involving noncancerous lesions and diseases which appear as enlargements of salivary glands whose etiologies are largely unknown. Included in this group are individuals with exocrine or endocrine disorders; children suffering from malnutrition; and disorders such as Mikulicz's syndrome and collagen disease.
2. Studies on salivary gland infections such as those associated with the cytomegaloviruses.
3. Studies on the biological importance of more than 30 proteins identified in saliva.

Dental Pulp Studies

Support of research on the dental pulp organ has for its purpose the improvement of our knowledge and information relative to the basic physiology, neurology, biochemistry and histology, both microscopic and ultramicroscopic, of dental pulp. A better understanding of the normal blood vascular dynamics and the neurohumoral factors which influence the pulp chamber are needed for the clinician, who may then better understand the clinical problems in pulpitis, and related pharmacological and analgesic regimens.

The inaccessibility and delicacy of the pulpal vasculature have made progress in the exact study of pulpal vascular dynamics very difficult. Traumatic operative procedures cause serious disturbances of pulp function and often render physical measurements meaningless. Scientists at Temple University School of Dentistry, under grant support from NIDR, are attempting to extend present knowledge on the functional innervation of the dental pulp vasculature. They are investigating the effects of atropine and various adrenergic blocking agents upon the depressor response produced by vagosympathetic stimulation. Experiments performed on anesthetized dogs showed that peripheral stimulation of the sympathetic portion of the severed vagosympathetic nerves depressed the intrapulpal blood pressure (IBP) in the maxillary canine. The vasodepression persisted in adrenergically depleted or blocked animals, but pressure was not affected after the administration of atropine. These findings suggest that a sympathetic, cholinergic mechanism might be activated in the dental pulp.

Research at the University of Iowa, reported in the FY 1971 annual report, concerning water-soluble peptides obtained from dental pulp is continuing. It had been reported that three peptides have been found to contain hydroxyproline, thus indicating their probable origin from collagen in the dental

pulp. Peptide number 2 (containing glycine-proline-proline) was subjected to chromatography using Sephadex G-15 to determine its molecular weight. It eluted just ahead of (glycine-proline-alamine) (M.W. 263) and behind penta-L-alanine (M.W. 373), indicating that its molecular weight is in the range of the tripeptide (glycine-proline-proline). This combination of amino acids comprises a relatively large portion of the collagen molecule. The findings strongly suggest that collagen is the origin of these dental pulp peptides. The same investigators have isolated three chemically different types of collagen in bovine dental pulp: (1) neutral collagen; (2) salt soluble collagen; and (3) an acid soluble collagen. Recent analysis of the salt soluble collagen, employing disc electrophoresis, has identified four bands tentatively designated as $\alpha 1$, $\alpha 2$, β and native collagen. This basic information will be valuable in understanding physiological changes in the tissue of the pulp chamber brought about by aging.

The need for information in this area is recognized. However, dental pulp studies is not one of the areas that has been designated by the NIDR for additional support; consequently, the program will continue at its present level.

I. INTRODUCTION

During FY 72, the General Oral Sciences Program continued to develop strength and diversity in its research and research training programs. Because of the nature of the General Oral Sciences Program, it encompasses more heterogeneity in its research activities than the other extramural program areas of NIDR which are directed more specifically at a particular categorical, disease-oriented problem. Special emphasis continues to be given to Pain Control and Dental Anesthesiology and significant progress was achieved in the initiation of new programs of research and research training in these areas.

II. SELECTED RESEARCH ACTIVITIES:

1. Research is continuing at the Medical College of Georgia to perfect a method to study capillary blood flow in oral tissues, especially the gingiva. This research may contribute to our understanding of the relationship of the oral microcirculation to various disease processes, including periodontal disease. Increased knowledge of how the oral microcirculation is regulated and the interplay of various environmental factors upon blood flow could be an important determinant of oral tissue health and resistance.

2. At the University of Louisville, investigators are exploring the hypothesis that carbonic anhydrase is an important factor in bone resorption. If this hypothesis is validated, new avenues for the therapeutic control of excessive bone resorption states may become available utilizing specific inhibitors of this enzyme. In progress now are experiments to develop a precise biochemical determination of the levels of carbonic anhydrase in bone coupled with a histological identification of the particular cell types that contain this enzyme.

3. An important research project is underway at the Medical College of Virginia to study the transport of various drugs into and out of saliva. This problem has some very practical implications for the use of drugs in the prevention and treatment of various oral diseases. It could also contribute to the utilization of saliva as a diagnostic fluid since correlation of drug levels in saliva and blood has often been disappointing and a better understanding of the salivary transport mechanisms could contribute markedly to improving this situation. Finally, this project could aid in the understanding, prevention and treatment of various drug-induced diseases of the mouth including gingival hyperplasia induced by dilantin and penicillin-induced black tongue.

4. A long-term clinical metabolic study of the complex interactions of fluoride with other minerals is continuing at Hines Veterans Hospital in Chicago. Results already obtained have clarified these interactions and will be of practical significance in the management of patients receiving fluoride supplements for therapeutic purposes. Furthermore, the study of fluoride-hormone interrelationships is relevant to the problem of osteoporosis. For example, information obtained in studies of the combined use of estrogen and

fluoride may aid in providing an improved modality of treatment for patients with post-menopausal osteoporosis. Data obtained on the effects of fluoride on mineral metabolism during corticosteroid administration may aid in preventing and retarding the development of corticosteroid induced osteoporosis. Finally, the study of the effects of fluoride on the calcium loss induced by acidosis may contribute to our knowledge of the role that acid base balance plays in bone metabolism and thus provide a more rational basis for the treatment of a variety of disease conditions associated with demineralization.

III. PAIN CONTROL AND DENTAL ANESTHESIOLOGY

A. Research

Relatively little research support has been provided in the past for studies related to pain and dental anesthesiology. During the past year two new research projects have been initiated and continued support provided to an ongoing study evaluating current methods of general anesthesia applicable to the dental situation. Definitive results on cardiorespiratory changes associated with dental general anesthesia and analgesia have already been obtained and efforts will now be directed to evaluating these changes in a larger and more diversified population as well as to studying in depth the recovery phases of dental anesthesia and analgesia.

A new research project initiated at the University of Washington in Seattle will evaluate the cerebral evoked potential responses to stimulation of the tooth pulp in normal volunteers and in patients undergoing restorative surgery. This work should contribute not only to a better understanding of the physiology mechanisms of pain sensation but will also have potential practical applications for the evaluation of analgesic drugs used in the treatment of dental pain. Furthermore, the availability of a physiologic measure of pain intensity will provide a tool for the investigation of relationships between pain sensation and pain perception.

Another new research project in the pain area is underway at the University of Michigan. Here, attention is directed at the trigeminal nerve which plays a major role in a number of important clinical facial pain syndromes. Many basic mechanisms operating in this nerve remain obscure. The investigator is attempting to shed more light on the sensory and reflex mechanisms of the trigeminal nerve in order to establish a better foundation for understanding its role in oral-facial reflexes and sensations, including pain syndromes such as trigeminal neuralgia.

B. Research Training

Significant progress has been achieved during the past year in the identification of centers of excellence for the research training of individuals motivated toward research and academic careers in pain control and dental anesthesiology. It is anticipated that one major training site will be established beginning July 1, 1972 and efforts are continuing to be aimed at the establishment of two or three additional sites for the following year. In addition, two new research fellowships have been funded to provide quality training in pain control to selected individuals.

C. Ad Hoc Committee Activities

A persistent and determined attempt has been made to examine and define the complex aspects of the pain and pain control problem as it currently exists in dental research, dental education and dental practice.

Two separate ad hoc committees have been involved in the effort. The first committee, a research and clinically oriented group, defined the various multifaceted elements of the enigma. The group also focused attention on the dental school, the hospital and other service organizations, as being the most vulnerable targets for achieving not only short range goals, but also greatly assisting in long range objectives.

The second committee, convened most recently, was composed of a group of selected dental educators, as well as scientists. They also addressed themselves to the broad issues of pain and pain control research and to the utilization of research and research-like endeavors in the improvement of undergraduate and graduate dental education.

Both committees commended the NIDR for the amount of visibility given the fledgling pain control program in the 5 Year Plan and highly recommended that a vigorous approach to all conventional grant mechanisms be attempted.

Since the dental school has been identified by both committees as a key issue in the existing problem, the NIDR was encouraged to explore the possibility of adopting an approach used by several other of the National Institutes of Health in dealing with sensitive and long neglected medical problems; as a consequence, the Institute was encouraged to study the feasibility of supporting both research and research related activities by granting Academic Awards to encourage and assist certain individuals in quality pain control programs at selected dental schools.

Report of the Director of Intramural Research
National Institute of Dental Research
July 1, 1971 to June 30, 1972

"A preface is like a front
tooth --- noticeable only
when missing."
R. F. Sognnaes

The report of the Director of Intramural Research has traditionally served as a preface to, and summary of, the more substantive research reports from individual intramural scientists. This year, a decision was made to revamp the format of the intramural annual progress reports so that wherever possible they would speak to sectional rather than to individual achievements. This change was undertaken on the basis of the notion that the constituent Sections of the Institute functionally encompass the purposes and research directions of the Institute as a whole and that, as a consequence, their summary statements of progress might best convey the accomplishments and satisfactions, as well as the problems which the past year's activities have provided.

Having reviewed the assembled sectional reports which immediately follow this introductory statement, the writer cannot help but be convinced of the advantages of this revision in style, since each report speaks so clearly both to the aims and the progress of the year's efforts. Paradoxically, in fact, the very effectiveness of this new mode of reporting makes it less necessary that these paragraphs provide the reader with a kind of editorial "arrow-pointing" toward those particularly significant advances in science which have occurred during the year.

There would be perplexity attached to the development of this report, therefore, were it not for the fact that the past twelve months seem to have been a period of great importance to the continuing evolution of our intramural program. For not only have substantive scientific advances been made during this period, but it has also been a time during which more and more of the Institute's scientific strengths have moved away from the realm of problem definition into the arena of problem solving. This latter turn of events, I believe, marks a significant turning point in the maturation of the Institute, one which is a direct and logical outcome of a research strategy which has been in force for over two decades.

At the time of its inception, twenty-four years ago, the primary tasks facing the Institute's intramural program were those concerned with the attainment of a body of carefully acquired scientific data, which could serve to put the then largely enigmatic problems of oral disease into a context comparable to others of man's afflictions. Secondarily, the program had to be so

organized as to permit exploitation of research leads having potential for application at the public health level. From the very outset, therefore, the intramural program was developed with a view toward maintaining a balance between fundamental research, i.e., that oriented toward problem definition, and research directed toward problem solving, i.e., that research activity which is commonly described as "developmental" or "applied."

A brief recollection of the state of knowledge concerning dental caries at that time will serve to demonstrate the nature and magnitude of the challenge facing the then nascent intramural program, and why initial emphasis was necessarily placed on problem definition as the proper strategy for achieving the Institute's goals. For even in the late forties, evidence supporting the notion that caries occurred as a consequence of microbial action was largely circumstantial. Preventive approaches of the day were primarily those pertaining to the maintenance of good oral hygiene, and avoidance of excessive sugar in the diet, and were based more on professional intuition than on solid scientific data. Moreover, at the public health level, efforts to promulgate these techniques of prevention were having little effect, as evidenced by the fact that almost all the nation's population suffered from the disease.

The anti-caries potential of fluoride ion, delivered in community water supplies or topically to the enamel surface, was just then beginning to become apparent. Evidence for its efficacy, however, was primarily derived from epidemiological studies, so demanding that a substantially greater research effort be made at the laboratory level to delineate the nature of its positive effects under rigorous experimental conditions.

To complete the picture, it may also be noted that, with respect to the other oral afflictions which comprised the Institute's area of mandate, i.e., periodontal disease, oro-facial growth defects, and oral soft tissue lesions, the situation was even less encouraging in terms of the then existing body of knowledge or fundamental understanding concerning them.

The Institute was thus faced with the need to develop a community of science which would focus on oral disease problems, with the first goal to be that of problem definition through the application of fundamental scientific approaches. Only to the extent that the state of knowledge warranted, was it deemed appropriate to bring into being a group of scientists devoted to problem solving. Accordingly, the early years of the intramural program saw the identification and recruitment of scientific staff whose primary contributions would relate to fundamental science, but whose efforts would in the long run bring oral diseases into some defined system which could then enable the development of rational approaches to their alleviation through more applied research.

Because the state of knowledge concerning etiologic and pathogenetic factors underlying dental disease was in such a chaotic state, a chaos born of dogmatism, inadequate hypotheses, insufficient observation, and a far too parochial scientific outlook -- all reflective of a dearth of well-trained investigators -- dental research was somewhat justifiably viewed by the scientific

community at large as a less than first-rate endeavor. An independent, but equally important challenge to the Institute, therefore, was that of establishing a working environment wherein scientific excellence was not only fostered but was to be the sine qua non.

Now, more than 20 years later, it is warrantable to assert that not only has this challenge been fully met, but that our community of intramural scientists has been perhaps the most important single factor in generating a status of full respectability for dentally-related research endeavors. This is not to suggest that other groups, in universities and elsewhere, have not contributed to this coming of age in dental research; but that our intramural program, which has been for many years and remains today the largest single concentration of dental research competence in the world, has served as the prime moving force. It may also be noted that the burgeoning of quality dental research, which can be observed in the private sector today, although largely a function of NIDR's past and current extramural efforts, not uncommonly also reflects the activities of scientists who at one time or another were members of NIDR's intramural staff.

The Institute's scientific productivity over the years, much of it couched in terms of fundamental disciplines such as biochemistry, microbiology, etc., has attracted large numbers of well-trained and enthusiastic staff from a variety of backgrounds. Of the nearly 100 people comprising our present professional research staff, for example, nearly two-thirds were trained at the doctoral level in fields other than, or in addition to clinical dentistry, and approximately one-fourth were trained as physicians. Active participation in dental research by an increasing number of physicians merits emphasis, since it signifies the Institute's success in calling attention to the many oral conditions which directly or indirectly reflect systemic disease states.

Traditionally, about 10 percent of our staff in any given year are individuals who have come to the Institute for two or three years' postdoctoral research training experience, and then move on to responsible positions in the academic community. As suggested previously, it is now commonplace to be able to identify the active role that these people (as well as former senior staff members) have had in generating foci of dentally-related research excellence where none had existed before.

Finally, the thoroughness with which our intramural research activities have become woven into the fabric of biomedical science can also be quantitated in terms of the fact that, of the 108 research projects currently being conducted in-house, the majority are being carried out in collaboration with investigators from other Institutes and Divisions of NIH, or with individuals or groups outside of government. Further, more than half of the 101 original research reports stemming from NIDR intramural activities during calendar year 1971 have been published in professional journals not primarily identified with dental concerns.

Clearly, therefore, there is ample evidence that the mode of conduct of intramural research in NIDR during the past twenty years has been profoundly

beneficial. Not only has it contributed measurably to an improved capacity to deal with dental ills, but it has also given rise to a substantial body of useful information in other health areas. Of equal importance, I believe, it has served to define and justify the position of distinction which dental research now occupies in the community of creative scientific inquiry.

The foregoing review of our intramural history and of our maturation as a community of scholarship provides the necessary backdrop against which to discuss substantive achievements, both present and past, which have resulted in our current ability to give increased attention to focused, problem solving research. As noted previously, the essential purpose of our earlier strategy, emphasizing problem definition, was to accumulate a body of fundamental knowledge which would provide a rational basis for the generation of hypotheses regarding etiology, and thus of more logical approaches to therapy and prevention.

Evolution of our present state of knowledge concerning dental caries is perhaps the prime example of the success of this approach. Over the years, major contributions to our understanding of caries have been made by intramural scientists, in concert with a growing community of scientists in universities and private research institutions. Collectively their work establishes the disease as being microbially mediated, but one in which susceptibility is determined by a complex interplay of host and environmental factors.

Through long and painstaking exploitation of germ-free animal techniques, it was shown that the organism Streptococcus mutans is the agent responsible for smooth surface caries. Further animal experimentation over the years also revealed that the disease is infectious and transmissible. Although by far the greatest bulk of experimental evidence accumulated thus far regarding the role of S. mutans in dental caries derives from animal experiments, there is a rapidly growing body of data drawn from clinical studies in man which tend to substantiate the thesis that S. mutans is equally important in human smooth surface caries. These research efforts have thus served to demonstrate that, from a microbiological point of view, dental caries fulfills Koch's postulates, so bringing it fully into the context of any of a variety of infectious diseases in man.

Unlike many of the latter, however, pursuit of the etiology of dental caries has resulted in the accumulation of a large body of information relating to environmental factors which may determine susceptibility and/or resistance to the microbial challenge. For example, systematic studies have confirmed the role of dietary sucrose in enhancing the pathogenicity of S. mutans. Sucrose appears to be the preferred nutritional substrate for the organism, and its metabolism yields not only copious amounts of lactic acid, which destroys the tooth substance, but also yields a viscous extracellular coating of polymeric carbohydrate which seems to facilitate adhesion of the organism to the surface of the tooth. Microbiological studies of the organism in pure culture, or in animal models, further suggest that substitution of sucrose by other dietary carbohydrates may decrease the production of this adhesive extracellular coating, so rendering the organism less pathogenic.

An independent but related approach to diminishing pathogenicity has involved utilization of the enzyme dextranase which, by selectively hydrolyzing the extracellular coating, also decreases its capacity to adhere to the tooth surface.

With respect to fluoride, it must honestly be stated that no full disclosure of the mode of action of this effective anti-caries agent has yet been developed. It has been demonstrated that the incorporation of fluoride ion into the hydroxylapatite mineral comprising dental enamel significantly reduces its solubility in acid. Accordingly it would appear that one possible basis for the protective effect of fluoride is that of decreasing the vulnerability of enamel to the effects of lactic acid produced by S. mutans and of other acid-producing microorganisms of the oral cavity. There are suggestions, however, that fluoride ion may also play a more direct prophylactic role by disturbing the normal metabolic behavior of oral microflora. Leads in this vein are currently being actively pursued within the Institute and elsewhere.

In the aggregate, these observations have stemmed from research oriented in terms of problem definition. They stand today as milestones in establishing a rational concept of the disease, and provide the basis for a multiplicity of applied research approaches to achieve equally rational preventive measures. The success of the problem definition phase of caries research has thus logically led to concerted efforts in problem solving. For not only are highly applied kinds of research now fully feasible, they are mandatory as logical expressions of the Institute's obligation to the public health. Accordingly, the Institute has now reassessed and restyled its organizational format, with the specific intention of devoting a substantial portion of its fiscal and manpower resources to an even more focused research attack on the caries problem. To this end the National Caries Program was established in 1969, and subsequently has undergone a rapid expansion. As of November, 1970, it was designated as an independent organizational entity within the Institute, and now constitutes the primary setting for undertaking applied caries research. To a significant extent it is currently staffed by scientists who formerly were directly involved in intramural research.

As the following intramural summary research reports will reveal, a substantial commitment of effort to caries-associated research problems still exists within the intramural program, despite the formation of the National Caries Program. For a large number of problems remain about the caries process which yet need to be defined rigorously through fundamental approaches. It bears emphasizing, however, that these intramurally conducted studies are being undertaken with the full knowledge of, and frequently with the collaboration of research staff of the National Caries Program. Thus, the establishment of a separate organizational component, charged with the responsibility of undertaking applied studies of means for alleviating the caries problem, has not and will not interfere with the longstanding scientific cooperation which has traditionally characterized the Institute's approach to research.

It is obvious that many years of wide-ranging and essentially undifferentiated research were required to accumulate the body of information which could be

utilized as a fundament for the present efforts of the National Caries Program. Therefore, it seems equally probable that the achievement of other goal-oriented scientific advances will continue to depend heavily on the maintenance of a viable community of science, oriented less immediately to problem solving than to problem definition. During the course of the past year, several lines of evidence have appeared which support the contention that this relatively unstructured approach is also yielding positive results with respect to periodontal disease.

Even casual comparison of previous years' summary research reports with those for this year will reveal a striking increase in the proportion of effort being devoted to definition of the etiologic and pathogenetic mechanisms involved in periodontal disease. More significantly, perhaps, this new emphasis is apparent in the description of the activities of a variety of intramural research units not heretofore identified with this particular area of endeavor; units in fact previously far more directed toward basic disciplinary science. As in the case of caries research, therefore, this phenomenon can be interpreted as reflecting the slow but deliberate development of a body of fundamental knowledge which now permits examination of the periodontal problem in a wholly reasonable context.

With respect to recent scientific advances in this regard, particular attention has been devoted to properties of periodontal plaque and to the microorganisms which it supports. Intramural research has previously shown that the area of the gingival sulcus harbors a particular micro-flora, a notable member of which is the filamentous diphtheroid, Actinomyces viscosus. While by no means the sole occupant of this micro-environment, A. viscosus appears to be the most probable microbial agent in the genesis of periodontitis, since, upon innoculation into germ-free animals, it produces a periodontal syndrome strikingly similar to the human disease. Studies during the year have revealed that a strain of a streptococcus, designated S4, elaborates a substance which inhibits the synthesis by A. viscosus of those extracellular products which, in part at least, facilitate its colonization of the tooth and adjacent gum tissues, so suggesting a potential route for development of a prophylactic technique based on microbial interaction. As might be anticipated, this avenue of research is being expanded and will be pursued actively during the coming year.

In another particularly striking research development, studies have been undertaken with respect to the immunogenic properties of dental plaque. This has been an especially rewarding enterprise in the sense not only of its outcome, but also because it has involved the joint efforts of two major units of the intramural program, and has required the input of a group of scientists whose respective backgrounds reflect primary training in dentistry, medicine and basic science. In essence it was demonstrated that dental plaque taken from human subjects exerts an immunogenic stimulus on normal human lymphocytes, as evidenced by induced proliferation in vitro. Moreover, plaque stimulation of lymphocytes provided by donors suffering from frank periodontal disease results not only in cell transformation, but also in production of soluble materials which are cytotoxic when added to fibroblast cell cultures, and which, when added to organ cultures containing bone,

significantly stimulate osteoclasis. Thus, for the first time, a biological basis may be emerging which will account for both the restricted but nonetheless profound destruction of soft tissues in periodontal disease, but as well the heretofore enigmatic loss of alveolar bone so characteristic of it. These findings are particularly appealing since a growing body of independent evidence is beginning to mount in support of the notion that a number of pathogenetic events in the evolution of periodontal disease are, indeed, attributable to the host defense mechanism, both humoral and cellular.

In summary, the foregoing research developments, as well as many others described in the summary reports which follow, seem to me indicative of the kind of conceptual shift in scientific emphasis which has been so evident during the past year. This shift is in my view a logical consequence of more than two decades of problem definition in certain areas of our research mission, and is the more welcome at a time when, as individuals, our investigators and supporting personnel seek personal satisfaction not only in science, but also in the context of serving the nation's health needs.

Report of the Computer Processing and Analysis Section*
National Institute of Dental Research
Summary Statement

Background

This section provides a centralized focus for the design, development and implementation of an on-line computer system, which serves a broad spectrum of research needs throughout the Institute's direct operating programs. Functionally, the section seeks to determine how the various intramural research efforts can be improved through the use of computer technology. Moreover, it provides the setting, both technical and intellectual, in which the investigator can expand the horizons of his research, ultimately permitting him to attempt experiments or pose questions which heretofore had not been amenable to exploration. The ability of the machine to perform simple repetitive operations at micro-second speed can serve substantially to complement the intuition, knowledge, and judgement of each researcher. Together, this man-machine synergism offers the prospect of significantly enhancing both the breadth and the efficiency of research at NIDR.

With the assistance of hardware and software specialists from the Division of Computer Research and Technology at NIH, the NIDR Computer system has been expanded to include the functions described below.

Progress During the Past Year

Applications

During the past year a gas chromatograph and a spectrophotometer have been interfaced with the system, serving the needs of the Environmental Mechanisms Section. An x-ray diffractometer is also now in the process of being interfaced to facilitate the activities of the Molecular Structure Section, Laboratory of Biological Structure. Similarly, the first steps have been taken in developing the techniques for the monitoring and control of bacterial growth, a prelude to the evolution of a fully automated "artificial mouth". Ongoing applications in neurophysiology, amino acid analysis, and liquid scintillation counting increased their computer utilization during the past year.

*This report is based upon progress achieved during the year in project numbers NIDR-IR-72-001-(a)-68 and NIDR-IR-72-002-(b)-72.

System

To meet the growing needs of the system, a H-316 minicomputer was interfaced to the resident DDP-516 system. This multiprocessor system will greatly facilitate the program development activity essential to the dynamic needs of a research environment by providing: 1. more core storage for running programs, 2. higher reliability for ongoing acquisitions and control processes, 3. more flexibility for system development and checkout.

Plans for the Coming Year

Development of closed-loop control experiments will represent a major involvement of the computer. Telecommunication with the NIH central IBM 360/370 complex will be implemented to provide more powerful computational capabilities for data acquired on the NIDR system. To facilitate the interpretation and analysis of data, an interactive graphics software package will also be put into service.

Report of the Environmental Mechanisms Section*
National Institute of Dental Research
Summary Statement

Background

The Environmental Mechanisms Section has the mission of investigating the interactions among cells and the interactions of cells with their environment. Interest has grown in characterizing physiological and biochemical adaptations of specific cells to their particular ecological situation. Considering the basic mission of the NIDR, the area appropriate for study by this section is the relationship between bacteria and the oral cavity. Specific studies have taken three main directions; namely: 1) the investigation of the metabolism and growth of oral streptococci 2) the development of a computer controlled system to simulate the oral environment, and 3) research on cellular slime molds in an attempt to understand the biochemical events accompanying aggregation and differentiation as an environmental response.

The first area of concentration has been that of studying the environmental role of various simple sugars and complex carbohydrates in the growth processes of cariogenic streptococci, especially Streptococcus mutans. Such information should contribute directly to the development of a system for physically simulating the natural environment of such organisms namely, the mouth.

The second area of research is an extension of the study of cariogenic streptococci, but incorporates modern computer technology. It is clear that many of the microbially mediated phenomena which take place in the mouth are the result of highly-complex, multiparametric interactions. Accordingly, an on-line computer system is being interfaced to control a fermentor in the laboratory in order to simulate oral conditions; in a sense comprising an "artificial mouth". By this technique, simultaneous multiparameter changes may be affected and multi-variate responses noted.
In a related effort, computer techniques are being developed

*This report is based upon progress achieved during the year in projects number NIDR-IR-72-008-(b)-(68), NIDR-IR-72-009-(b)-(72), NIDR-IR-72-010-(b)-(60), NIDR-IR-72-011-(a)-(71), NIDR-IR-72-012-(a)-(71), NIDR-IR-72-013-(b)-(71), NIDR-IR-72-014-(b)-(71), NIDR-IR-72-015-(a)-(71), NIDR-IR-72-016-(a)-(71), NIDR-IR-72-017-(a)-(72).

to permit a uniform coding system for describing bacteria. This system will become the foundation of an vitally important international microbial data bank.

The third area of research has been that of studying the biochemical and environmental control of differentiation in the cellular slime mold, or social amoeba, Dictyostelium discoideum. Of particular relevance is that a number of cellular properties of D. discoideum are strikingly similar to those noted during certain stages of differentiation in mammalian species.

Progress This Year

Growth and Metabolism of Oral Bacteria

When grown in the presence of sucrose, S. mutans forms extracellular glucans and fructans. Assessment of the proportion of sucrose carbon converted to each of these polysaccharides resulting from the biological activity during growth of S. mutans was done by using sucrose labeled in either the glucosyl or fructosyl moieties as a substrate. While only a few percent of the sucrose administered finds its way into polysaccharide, 90% being converted to lactic acid, the distribution between glucan and fructan varies widely amongst strains of S. mutans. Glucan is the predominant (sometimes exclusive) polysaccharide, but one strain (1B1600) produced 30% fructan. Thus, plaque formation by S. mutans is accomplished with only a small portion of the available sucrose used for polysaccharide formation.

An important consideration in the impact of the micro-environment on these cocci is the study of the various enzymatic systems responsible for the initial attack on the sucrose molecule. Presumably, all the mechanisms have the cleavage of the glycosidic bond of the sucrose in common, irrespective of the nature of the products resulting from that cleavage. Thus, we are beginning the purification of polysaccharide-producing enzymes. The invertase activities are also being isolated for further characterization. To help in the characterization, new techniques for making specifically labeled sucroses have been developed.

When cariogenic streptococci are grown in the presence of sucrose the use of classical turbidimetric techniques for the determination of cell number is complicated by the production of insoluble glucans and cell aggregation phenomena. In order to devise a reliable index of cell number by measurement of DNA, a fluorometric assay procedure using ethidium bromide was developed. The method is applicable to measurement of

bacterial cellular DNA in pure cultures, even in the presence of dextran, as well as in human dental plaque. It is 100-fold more sensitive than the conventional colorimetric procedures.

The study of growth kinetics of S. mutans in a fermentation requires close monitoring and control of the environmental pH of the cells since it is known that the pH of the fermentation affects the growth rate. Therefore a pH-monitoring system, suitable for use with an on-line computer, was developed. It is insensitive to the grounding problems which prevent accurate pH determination with conventional pH meters in grounded solutions. As many as three specific ion electrodes can be used at the same time in the system, thus allowing multiparametric continuous monitoring of the fermentation. In order to complete the control loop, computer-controlled pumps are used to pump acidic or basic solutions into the fermentation. The pump-control interface can handle as many as thirty-two pumps at once.

The Use of Computer Technology

The second area of investigation, carried out with the close cooperation of the Computer Processing and Analysis Section, is related to the first in that it involves the methods of using computers to study the oral bacteria. Many innovative continuous monitoring transducers are necessary to fully implement a control system. For example, in order to measure turbidity in microbial cultures with an on-line computer, a prototype autoclavable turbidity probe has been built. It uses a red light emitting diode as a source of light. The light is transmitted in and out of the culture by image conduit. A PIN photodiode is used as the light sensor. A special dual amplifier circuit is used to match the output range of the photodiode to the input of the computer to maximize the sensitivity throughout the normal bacterial growth range.

Procedures were developed to acquire data from the gas chromatograph and automatically return processed data to the investigator. The Gilford spectrophotometer was interfaced with the same computer. A complex set of modular programs is in various stages of development for the multiplicity of uses possible with this instrument, including enzyme kinetics, end-point assays, scanning densitometry, spectral analysis, etc.

In depth studies of the ecological distribution and epidemiology of oral microorganisms require the handling of microbial strain data by large scale computers. Definition and standardization of the questions that are asked about microbial strains in a computer-compatible form is the first goal. Programs are being developed to enter data and retrieve it in a

variety of ways for epidemiological, diagnostic, taxonomic, and ecological uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers.

Aggregation and Differentiation in Dictyostelium discoideum

The transition from single amoebae to a multicellular organism such as occurs in the differentiation of the cellular slime mold, D. discoideum, provides an elegantly discrete model for studying the control of chemotaxis, the process by which individual cells aggregate toward a common center. Cyclic AMP has been implicated as the agent responsible for chemotaxis in D. discoideum.

Recently, we have been studying the role of the cyclic nucleotide phosphodiesterase which destroys cyclic AMP, postulating that this enzyme might be an obligate part of the differentiation process. We had previously shown that high levels of cyclic AMP could prevent the completion of differentiation, suggesting that a specific and precisely controlled mechanism for the destruction of cyclic AMP would be required to achieve normal development.

Purified antibody against the cyclic nucleotide phosphodiesterase was prepared and was incorporated into the cell suspensions of D. discoideum before they were placed on agar. By repeating the experiment using filter membranes as the support medium for the cells instead of agar, we could first place the cells on a pad containing antibody solution and then move the membranes and cells on to a pad without antibody. The liquid in the second pad served to dilute the antibody in the cells' environment. The cells did not differentiate for the five days they were in contact with the antibody, but did so when the antibody was removed by dilution. The inhibition by antibody is reversible. Thus, the enzyme is indeed an obligate part of the aggregative system in D. discoideum.

In studying the enzyme itself, it was possible to demonstrate that at least two of the multiple forms of the enzyme could be interconverted by adding dithiothreitol, or by allowing auto-oxidation to occur. Such interconversion may well play a role in the further differentiating process since the various forms have differing abilities to destroy cyclic AMP. To elucidate this dependence on the phosphodiesterase, work is in progress in two related areas. The first is the control of this extracellular enzyme by environmental conditions such as metal ions and metabolites, and the second is the effect on the amoebae of the product of the phosphodiesterase reaction, i.e., 5'-AMP.

Since mononucleotides (which are the products of the reaction by which the cyclic nucleotides are destroyed) specifically accelerate the rate of differentiation, we are studying their metabolism by studying the fate of isotopically labeled mononucleotides in aggregating D. discoideum. It appears that the pathways are relatively simple. Using paper chromatography it is evident that few metabolites are generated from the original substrates. However, some of these compounds remain unknown at this time and are the subject of current investigation. By knowing the nature of the metabolic pathways for mononucleotides in these cells we hope to be able to pinpoint the rate controlling steps.

Report of the Neural Mechanisms Section*
National Institute of Dental Research
Summary Statement

The Neural Mechanisms Section was established to study neural mechanisms of sensation and movement in the oral-facial region. In the last few years, the major efforts of the Section have focused on the structure and function of the trigeminal brain stem nuclear complex. We have found that sensory information from the face and mouth, travelling as neural impulses in the various branches of the trigeminal nerve, is subject to considerable modification and processing at the level of the trigeminal brain stem nuclei, the first central relay to higher centers in the brain. Neuronal input from various regions including the cerebral cortex and the reticular formation alter the activity of trigeminal brain stem neurons. Our anatomical studies have provided a structural basis for such sensory interactions. In addition to the presence of incoming fibers from other central nervous system structures, the most common neural elements are neurons whose axons never leave the nuclear complex but instead communicate via synapses with other intranuclear cells.

A lesion in man or monkey which interrupts connections between the rostral and caudal poles of the trigeminal brain stem nuclear complex, or decreases trigeminal nerve input to the caudal nuclei results in decreased sensitivity on the face to painful and thermal stimuli. The physiological mechanisms underlying these behavioral observations are poorly understood. Studies in many laboratories over the past fifteen years have failed to reveal a significant population of neurons in this complex which respond only to painful or thermal stimuli. Our present studies are designed to further elucidate the anatomical organization and brain stem mechanisms responsible for the transmission of information about pain and temperature to other parts of the central nervous system.

Progress During the Past Year

Anatomical Studies

During the past year our efforts have been directed toward a detailed analysis of the neurons of both the main sensory and spinal trigeminal nuclei, and the intranuclear course of their

*This report is based upon progress achieved during the year in project numbers NIDR-IR-72-003-(b)-(70), NIDR-IR-72-004-(a)-(70), NIDR-IR-72-005-(b)-(65), NIDR-IR-72-006-(b)-(66), NIDR-IR-72-007-(a)-(69)

axons. This analysis has been carried out utilizing two different techniques. Firstly, light microscopical analysis of one micron sections of specimens embedded in epoxy resin has permitted direct visualization of all neuronal cell bodies and myelinated axons which are present in the plane of section. These same preparations have also been used in conjunction with experimental degeneration procedures, in which both degenerating and surviving axons may be compared in the same preparation. Secondly, the rapid Golgi method has been used to study the dendritic arborization and axonal trajectory of main sensory nucleus and spinal trigeminal nucleus neurons.

Numerous small compact bundles of axons (the deep bundles) run longitudinally through the entire spinal trigeminal nucleus. These bundles are tightly packed in nucleus oralis and spread out in a looser arrangement both in nucleus interpolaris and in the magnocellular layer of nucleus caudalis. They form a distinct band in the substantia gelatinosal layer of nucleus caudalis. Each bundle contains approximately one thousand axons, the ratio of myelinated to unmyelinated axons being approximately 1:1. Eighty to ninety percent of the myelinated axons are between 0.3 and 1.5 microns in diameter. The individual bundles are laced together in an extensive plexus by small groups of axons crossing from one bundle to another.

Examination of these bundles six and thirty days after trigeminal nerve rhizotomy reveals that each contains only a few degenerating trigeminal nerve axons, the larger of which are usually found in the periphery of the bundles. These experiments reveal that the vast majority of axons in the bundles, and in the spinal tract as well, survive trigeminal nerve rhizotomy; hence they are not part of the sensory root of the trigeminal nerve.

In order to assess the number of axons which ascend within the deep bundles from nucleus caudalis to more rostral levels of the spinal trigeminal nucleus, the spinal trigeminal nucleus was transected at the level of the obex. Examination of the bundles rostral to the point of transection, at survival times of five and twelve days postoperatively, revealed many degenerating small myelinated axons in the bundles. Most of these ascending axons lie in the center of the bundles.

In another experiment the spinal trigeminal nucleus and tract were transected at the level of nucleus oralis in order to assess the number of descending axons in the deep bundles. After 5 days, the deep bundles, caudal to the point of transection, contained numerous degenerating small myelinated axons. Most of these descended in the periphery of the bundles. The number of degenerating axons in the bundles were much more numerous after this transection than after trigeminal

nerve rhizotomy, and most of them apparently are derived from neurons within the main sensory trigeminal nucleus and rostral portion of the spinal trigeminal nucleus. Rapid Golgi experiments also revealed that many neurons of the spinal trigeminal nucleus send their axons into the deep bundles where they may ascend or descend. The axons of some spinal trigeminal neurons on entering the deep bundles divide in T shaped fashion to send one branch rostrally and one branch caudally.

These studies on the structural organization of the trigeminal brain stem nuclei suggest that the major role of the caudal pole of the spinal trigeminal nucleus is to modify the neuronal activity of rostrally located trigeminal brain stem neurons. Many of the neurons in the rostral trigeminal brain stem nuclei project to other parts of the central nervous system, whereas the caudal pole of the nuclear complex consists mainly of intranuclear neurons. The interaction between these two main subdivisions of the trigeminal nuclear complex may play an important role in the transmission of information about painful and thermal stimuli, since our perception of these sensations from the face and mouth is dependent on connections between the rostral and caudal poles. The physiological studies described below are designed to test this hypothesis.

Physiological Studies

Our first concern was how sensory information about temperature and pain reaches the trigeminal brain stem nuclear complex. How do the trigeminal nerve fibers innervating the face and lips of the monkey respond to thermal and painful stimuli? Previous studies suggested that small myelinated and unmyelinated fibers were involved, necessitating the perfection of techniques which allowed us to surgically dissect fibers and record their electrical activity. In addition, we wanted to quantify the responses so that they could be compared with the response properties of central trigeminal system neurons. For this purpose a thermal probe was developed to deliver precisely controlled temperature stimuli. Feedback and control systems maintain and vary the probe temperature, while also permitting step temperature changes of ten degrees per second. The probe temperature range is twenty to sixty degrees Centigrade, so enabling the investigator to deliver controlled noxious heat stimuli.

Detailed quantitative analysis of the response properties of these fibers was enhanced by utilization of the NIDR computer system. The neuronal spike discharge data is stored on magnetic tape in the laboratory and also can be transferred on-line to the disc storage area of the computer after amplification and conversion to digital pulses. Computer

software has been developed to access the data from the disc and to process it. Summary response data is displayed graphically in the laboratory and the investigator can change the stimulative parameters applied to the monkey's face while recording from the same fiber.

Our present data indicates that single fibers which increase their activity to cooling, warming or noxious heat originate in the hairy or glabrous skin of the face and oral mucosa of the monkey. The receptive fields of these fibers are single spots one millimeter or less in diameter. Conduction velocity measurements indicate that this is a population of small myelinated and possibly unmyelinated nerve fibers. The "cold" fibers are sensitive to changes in temperature of less than one degree and respond over a temperature range from forty degrees to less than twenty degrees Centigrade. The pattern of activity shifts as the spot is cooled, irregular bursts of spike discharge being quite prevalent. "Warm" fibers are less numerous, and appear to conduct more slowly than do most cold fibers. They respond to small temperature shifts in the range of thirty-eight to forty-five degrees Centigrade with a very regular discharge pattern. "Noxious heat" fibers are quite similar to warm fibers, and respond in the range of forty-five to fifty degrees Centigrade. Occasionally, cold fibers will also respond in the noxious heat range.

The second question we asked concerns the response properties of trigeminal brain stem neurons to similar stimuli. How do these responses compare with those of the incoming trigeminal nerve fibers? Is there a convergence of more than one fiber type on a given brain stem neuron? In order to rule out the effect of anesthesia and extensive experimental surgery on such responses, these experiments are to be performed on awake, restrained monkeys. The animal will be trained to indicate whether the stimulus is cold, warm or painful, and to turn off a pain stimulus if it is too intense. Thus, in a manner similar to human experiments on pain the animal will control the level of pain he is able to tolerate. Microelectrodes and a combined mechanohydraulic microdrive assembly have been developed during the year to facilitate single-unit recording procedures in the trigeminal nuclear complex. Animals also have been trained to make temperature discriminations in the warming and cooling directions.

Future Plans

Our aim is to train monkeys to make behavioral discriminations of cold, warm and pain stimuli while simultaneously recording the activity of trigeminal brain stem neurons responsive to such stimuli. This will establish which parameters of the response are directly related to the behavioral discrimination.

The responses of neurons in the rostral and caudal parts of the trigeminal brain stem nuclear complex, and their correlation with behavioral discriminations, will be compared before and after a trigeminal tractotomy operation. Our ultimate aim is to modify pain thresholds in the monkey, utilizing nonsurgical methods which mimic the effects on trigeminal brain stem neuronal activity produced by the above surgical procedure.

Anatomical studies will elaborate on the structure of the neurons of the trigeminal nuclear complex and their interconnections. The dendritic arborizations of the neurons in the various subdivisions will be compared in rapid Golgi preparations. Electron microscopical studies will be extended to the caudal spinal trigeminal nucleus and to a group of neurons embedded in the spinal trigeminal tract.

Report of Experimental Pathology Branch
National Institute of Dental Research
Summary Statement

Organized in 1969 to respond to what was seen then and remains today an important programmatic need to undertake research at the interface between clinical disease and laboratory experiment, the Experimental Pathology Branch has continued during the past year to make substantive progress in a variety of research endeavors. Of the various programmatic segments of the NIDR intramural programs, this Branch has been affected perhaps the most by our continuing personnel restrictions. Thus, since its inception, the Branch has lost 3 of its professional staff, including its chief, and there have been no opportunities subsequently to rectify the deficit. Despite this adversity, however, the following paragraphs reveal that the remaining cadre of 5 investigators and 10 supporting personnel have enthusiastically maintained impetus in their pursuit of relevant research goals. Moreover, the Branch personnel have also extended their involvement in collaborative functions, and by so doing have not only enhanced the research activities of other segments of the Institute, but have also thereby facilitated the execution of their own research interests.

During the course of the past year, as a logical facet of the Branch's mission of developing an orderly and systematic characterization of precancerous lesions of the oral mucosa, the Diagnostic Pathology Section has accumulated further case information and specimens for histochemical analysis from patients with "snuff-dipper's" keratosis, and from those with inflamed oral mucosa consequent to chronic denture irritation, both situations which may predispose to oral neoplasia. Histochemical studies undertaken thus far have revealed striking accumulations of glycoprotein in the subepithelial lesion associated with the former condition, and in the latter the accumulation of sulfhydryl-rich material in degenerating epithelium.

During the year also the Diagnostic Pathology Section has continued to play an active role in relation to clinical diagnosis. Thus, some 660 accessions of human material were processed and diagnosed, reflecting inputs from NIDR's Dental Clinic as well as from a number of Federal health agencies across the country. An additional 313 accessions stemmed from animal research undertaken either by investigators at NIDR or elsewhere at NIH. During this same time the Laboratory of Pathology, NCI, acting as the central file for pathologic specimens at the Clinical Center, catalogued 3,166 new surgical specimens, including the 660 oral pathology specimens referred to above. Thus, approximately 21% of the NCI pathology accessions were routed from NIDR's Diagnostic Pathology Section.

The Oncology Section has also continued to explore the role of environmental variables as predisposing influences in the genesis of oral cancer. Specifically, the past year has seen the continuation of studies in the baboon concerning the oncogenic potential of betel quid, the widespread use of which in India and Southeast Asia has been strongly implicated epidemiologically with human oral cancer. Implantation of betel quid in the cheek pouch of

baboons over a period of 48 months has led to the occurrence of gross lesions characterized histologically by marked epithelial atypia, epithelial hyperplasia and encroachment into the underlying lamina propria. While no evidence of frank invasiveness has yet been noted, this histopathological picture is highly suggestive of carcinoma *in situ*.

The Oncology Section, which has been physically based at the Southwest Foundation for Research and Education, San Antonio, Texas, during the past three years, has also been charged with the programmatic responsibility of executing research on the biocompatibility of candidate materials for use as tooth and/or bone substitutes. Results during the past year suggests that porous calcium aluminate implants elicit little or no adverse host response and that the pores become invaded by blood vessels, connective tissue and bone. It is proposed that these studies will be continued and expanded by collaborative contract, although the geographic locus of the Oncology Section will return to the Bethesda campus during the summer of 1972.

The Oncology Section also continues to function as a Collecting Center for the W.H.O. International Reference Center, the focus of which is to study and classify oral premalignant epithelial lesions on an international basis. Partly in association with the latter, the Section has also been effectively active in a PL480-sponsored study of oral cancer and precancerous states in India. Progress in this collaborative program, which is now in its 7th year, has been summarized during the past year by publication of a comprehensive report in book form.

In accord with its charge to focus on the interface between clinical and experimental disease, the scope of the Branch also includes fundamental studies relating to disease mechanisms. Thus, the Histochemistry Section has been primarily concerned with cytochemical and histochemical parameters of metabolic disturbance as a function of pathophysiology. The report which follows describes the relatively wide ranging interests of this Section and points particularly to their increasing interest in studies of immediate interest to clinical dental problems. These include characterization of immunofluorescence of human dental plaque with specific respect to occurrence of the immunoglobulins IgG and IgA. Current evidence indicates that the distribution of the former is random in the plaque while the latter appears to be localized to its oral surface.

As in the case of the other Sections comprising the Branch, the Histochemistry Section is much involved in collaborative research enterprises both within and without NIDR, and, in concert with NIDR's intramural programs generally, is utilizing the collaborative contract mechanism on a broader basis than before in order to enhance the effectiveness of its limited personnel.

Finally, it bears emphasis that even in the face of limited resources, the professional cadre comprising the Branch have contributed to the genesis of 1 book, 15 manuscripts and 3 abstracts during the year. Moreover, their recognized expertise in the field has led to their participation in a variety of national meetings and workshops as well as invited participation in international symposia.

Report of the Diagnostic Pathology Section
National Institute of Dental Research
Summary Statement*

The primary function of this Section is to perform service and research activities relative to the diagnosis and study of oral pathologic processes in human beings. Created in June, 1969, the Section is concerned with recording, processing, and appropriate documentation of human oral tissues submitted for pathologic examination from intramural and extramural Public Health Service sources, and the use of this material for research, clinicopathologic correlations, longitudinal study of oral diseases and the application of established techniques, such as histochemistry, electron microscopy, immunogluorescent procedures, etc., to these tissues.

The primary emphasis of the Section is the development of data correlating clinically-observed changes with the microscopic observations in various oral tissues. Those areas of current clinicopathologic interest include studies of oral mucosal diseases, the dentition in acquired and inherited metabolic diseases, and minor salivary gland disorders. In collaboration with the Institute's Histochemistry Section, clinicopathologic studies of human oral mucosal diseases have recently emphasized the use of histochemical approaches to further characterize some of the changes observed in certain clinically unique oral disorders. For example, we have examined an unusual change noted in the superficial epithelium of chronically inflamed oral mucosa commonly associated with chronic denture irritation. This was identified histochemically as being rich in sulfhydryl groups and representing a degenerative epithelial alteration. These observations warrant further investigations of the local oral environmental factors as they relate to the morphologic changes observed in these tissues.

Histochemical studies of subepithelial deposits associated with "snuff-dipper's keratosis" has revealed that these represent an unusual glycoprotein, and not amyloid as previously reported. Their occurrence in association with a particular type of snuff ("Copenhagen" brand of U. S. Tobacco Co.) further emphasized the need for clinicopathologic investigations, since "snuff-dipper's keratosis" is known to predispose to "snuff-dipper's carcinoma."

Clinical studies of deciduous and permanent teeth showing alterations associated with metabolic diseases have been pursued; however, access to histologic materials has proved to be a problem because of the limited availability of teeth for study. Permanent teeth generally are not available unless removed for periodontal disease, caries, impaction, etc., while deciduous teeth constitute a more readily accessible reservoir for study.

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*This report is based upon progress achieved during the year in Project Nos. NIDR-EPB-003-(a)-63, NIDR-EPB-72-004-(a)-66, and NIDR-EPB-72-005-(a)-70.

Teeth from patients with various metabolic disorders, especially those patients under study at the Clinical Center, are considered most desirable. Of particular interest are teeth from patients with hereditary hypophosphatemia, hypophosphatasia, pseudohypoparathyroidism, and infantile hypercalcemia.

The clinical and morphologic studies of minor salivary gland disorders have centered chiefly on histologic changes seen in Sjogren's syndrome and reflect a particularly successful collaborative research effort between investigators from NIDR and those affiliated with the Arthritis and Rheumatism Branch of the National Institute of Arthritis and Metabolic Diseases. The minor salivary gland biopsy has been clearly shown to be an essential parameter in the diagnostic evaluation and therapeutic follow-up of these patients, and is being pursued further for its utility in other disorders such as lupus erythematosus, sarcoidosis, and other connective tissue disorders.

Application of immunofluorescent procedures to salivary gland tissue using sera from patients with Sjogren's syndrome has indicated the presence of antigenic sites in the ductal-periductal region. This technique has correlated with autoradiographic procedures performed by Dr. Norman Cummings of the Oral Medicine and Surgery Branch of NIDR, demonstrating the specificity and stability of the isolated and radiolabelled gamma globulin fraction from the serum of a patient with Sjogren's syndrome.

Future plans center on the continued development of data correlating clinical and morphologic changes and the utilization of research techniques on these tissues. The purpose is to further our understanding of pathogenetic mechanisms of human oral mucosal diseases, dental alterations in metabolic disorders, and morphofunctional changes in salivary gland diseases. Several areas that need to be further developed include genetic and epidemiologic data as it relates particularly to the oral mucosal and dentitional studies. Continuation of the salivary gland studies and the collaborative efforts with the Arthritis and Rheumatism Branch and intramural (NIDR) groups are necessary for further elucidation of the anti-salivary duct antigen. There are also many opportunities to collaborate with clinical as well as experimental investigations both intramurally and extramurally; however, the routine service activities of the Section necessitate only selective support for these studies. The Sectional activities will continue to provide consultative and professional liaison with the Laboratory of Pathology of the National Cancer Institute, as well as formal lectures and liaison with the Armed Forces Institute of Pathology, the U.S. Naval Dental School, Georgetown University and Howard University Dental Schools and the Smithsonian Institution.

Report of the Histochemistry Section
National Institute of Dental Research
Summary Statement*

Histochemistry evolved from the biologists', anatomists', histologists', and pathologists' attempt to relate substance to structure and function, and while it is classically envisioned as a morphological tool, the working definition of histochemistry employed in this Section includes a wide range of methodology in the study of the qualitative and quantitative chemistry of tissues. Histochemical, biochemical and cell and tissue culture studies have evolved from several lines of inquiry with the intent of further understanding the physiologic and pathologic processes occurring in oral tissues. While the emphasis has been placed on periodontal disease, the results of these studies have had a much broader range of applicability. It has been demonstrated that the histochemical approach, when employed in proper relation to other disciplines, provides a unique view of biological processes.

In keeping with the multiple disciplinary approach of this section, progress during the year and its significance will be considered under four separate headings.

1. Biosynthesis and degradation of acid mucopolysaccharides

SV40 transformation of 3T3 fibroblasts produces a marked decrease in the rate of synthesis of acid mucopolysaccharides when compared to the parent cell line. However, when such transformed cells are grown in a medium supplemented with dibutyryl-cyclic AMP and theophylline for three days, synthesis and secretion of acid mucopolysaccharides occurs at a rate comparable to control cells. From examination of the kinetics of this effect, it appears that it is due to an increase in the differential rate of acid mucopolysaccharide synthesis; that is, the rate of acid mucopolysaccharide synthesis based on the rate of cell protein synthesis. Biosynthesis of acid mucopolysaccharides is also markedly affected during parathyroid hormone induced bone resorption. It was found that cells of resorbing bone synthesize hyaluronic acid at a much greater rate than the controls. The specific cells responsible for this activity have not as yet been determined. The knowledge of the metabolism of the connective tissue acid mucopolysaccharides is of considerable importance since disruption of this metabolism results from several diseased states. Thus, as a class of compounds acid mucopolysaccharides are of increasing biological interest since new studies indicate that they may be involved in cell to cell interaction as well as having structural functions.

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*This report is based upon progress achieved during the year in Project Nos. NIDR-EPB-72-001-(b)-(64) and NIDR-EPB-72-002-(b)-(66).

2. Histochemical study of dihydroorotic dehydrogenase in oral tissues

In human and rat gingiva, intense dihydroorotic dehydrogenase activity occurred in the proximal regions of the basal epithelial cells and in the perinuclear region of cells in the prickle cell layer. In the crevicular epithelium, enzymatic activity was localized in the basal cells. In the rat jaw, osteoblasts, young osteocytes and cementoblasts were stained intensely, while fibroblasts and cementoblasts were only moderately stained. Variations in enzymatic activity in the jaw could be correlated with the amount of active remodeling. In the developing tooth, the staining pattern varied with the state of differentiation of the inner enamel epithelium. Undifferentiated cells were stained diffusely whereas fully functional ameloblasts were stained most intensely in the basal areas. While it is premature to attempt interpretation of the activity distribution so obtained in terms of the intermediary metabolism of pyrimidines in a given tissue, the concentration of activity in certain cells is consistent with the concept of increased requirement for nucleic acid synthesis in these cells.

3. Folic acid deficiency studies

Studies in establishing folic acid deficiency states in animals (intramural) have demonstrated the feasibility of using the laboratory white rat as an experimental model to demonstrate the specific morphologic and chemical changes which take place in oral epithelium associated with folic acid deficiency states established by dietary conditions and states of stress. In a collaborative pilot study (Dr. H. Spencer, Metabolic Section, Hines V.A. Hospital, Hines, Illinois), it has been demonstrated that human volunteers undergoing a period of starvation go into acute folic acid deficiency upon re-feeding. The significance of these findings is related to the fact that in experimentally induced folic acid deficiencies, epithelial changes include interference with the maturation of epithelial cells, impairment of keratinization with an increase of susceptibility to ulceration and secondary infection.

4. Human dental plaque studies

A technique for cutting fresh frozen sections of human dental plaque on mylar strips has been devised which permits the study of such sections by enzyme and fluorescent antibody histochemical techniques. All of the dehydrogenase enzymes thus far studied are present in bacterial colonies. Fluorescent antibodies directed toward various immunoglobulins have resulted in a demonstration of the presence of IgG and IgA in human dental plaque of five to ten days of age. IgG appears to be randomly distributed throughout the plaque and is associated with viable and non-viable bacterial colonies. IgA on the other hand, appears to be localized to the superficial layers. These results are significant in that they are contributions to the knowledge of the biologic nature of human dental plaque.

During the coming year, histochemical, biochemical and cell and tissue culture investigations will continue. The areas of specific interest will be the metabolic analysis of normal and diseased tissues as revealed by qualitative and quantitative enzyme and end-product histochemistry. Thus, studies on acid mucopolysaccharides will be extended with the objective of defining the mechanisms of action of selected factors which affect their synthesis and degradation. Similarly, folic acid deficiency studies will continue in animals and in humans to demonstrate specific metabolic defects in oral cells.

The contract mechanism is being considered to provide support for a collaborative project with Dr. H. Spencer, Hines V.A. Hospital, Hines, Illinois, using human volunteers on a closely controlled folic acid study, and a contract is planned for the electron microscopic localization of certain hydrolytic enzymes in the periodontal ligament of the rat. A collaborative study with Georgetown University and the U.S. Navy Dental School will continue to provide information on oral changes associated with folic acid deficiency states in pregnant females, while a collaborative project with Georgetown University involving human dental plaque will also continue. Such plaque collected on mylar strips will be subjected to enzyme histochemical studies and fluorescent antibody staining for specific immunoglobulins.

Report of the Oncology Section
National Institute of Dental Research
Summary Statement*

Oncology Research

The Section of Oncology has approached its main research interest - oral cancer - along three avenues. First, the most productive of these in the clinical sense has been the P.L. 480 funded epidemiological oral cancer study in India. The extenstive scientific findings from the first six years work has now been reported in book form (1). In November, 1971, papers were presented by Dr. Mehta, Dr. Hamner, and Dr. Daftary at the IV Indian National Cancer Conference in Bangalore.

The second chief thrust has been in the field of histopathology. The Section of Oncology was designated as a Collecting Center for the W.H.O. International Reference Center in Copenhagen to participate in a collaborative, international effort to study oral premalignant epithelial lesions and arrive at a common terminology. We have contributed cases and continue to participate in this mutual endeavor (2,3). Similarly from the histopathological viewpoint, the Section continues to collect data on fibro-osseous jaw tumors, which will also be tabulated in book form.

The third effort lies in basic research on betel quid carcinogenesis supported under N.I.D.R. contract funding at the Southwest Foundation for Research & Education in San Antonio, Texas. Gross lesions, demonstrating marked epithelial atypia, have been produced in the baboon cheek pouch mucosa after 48 months of exposure to betel leaf, areca nut, lime, and tobacco (4). This basic research study supports the clinical findings in our Indian project patients. This study is described in greater detail in the contract's annual renewal report.

During 1971, Dr. Hamner made two working trips to India. In the coming year Dr. Mehta and Dr. Pindborg will visit the United States for consultation on the P.L. 480 project and with Dr. Hamner will present papers at a Conference on Oral Oncogenesis in Birmingham, Alabama in November, 1972.

The Indian P.L. 480 Project has been continued for an additional three years April, 1972-1975. It is hoped to complete the book on fibro-osseous lesions during 1972-73. The betel quid carcinogenesis study in baboons will be continued for another year, half of the animals with gross lesions being removed from treatment to note if their lesions regress, progress, or remain the same.

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*This report is based upon progress achieved during the year in Project No. NIDR-EPB-72-006-(c)-(66), Contract Nos. PH-43-67-1475 and PH-43-67-1476, and P.L. 480 Project No. #01-022-1.

Implant Biomaterials Research

These investigations have been conducted as direct contracted research with the Southwest Foundation for Research and Education. The detailed reports for this contract have been channeled through the Science Information Exchange. In brief summation, the artificial tooth implantation studies have encompassed ceramic, plastic, and pyrolytic carbon tooth or bladevent replica implantation in the jaws of baboons. Clinical, radiographic, and histopathologic evaluations have been made in regard to each of these replacement biomaterials (5-0).

In the forthcoming year research under this contract will focus on metal and pyrolytic carbon bladevent insertion into sub-human primate jaws and the use of calcium aluminate and calcium phosphate ceramics for periodontal osseous defect obliteration.

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Report of the Human Genetics Branch
National Institute of Dental Research
Summary Statement

The program of the Human Genetics Branch is oriented toward investigations relating to the genetic basis of variation in oral structure and function, as well as to problems of more general genetic interest. The Branch is divided administratively into two sections; Developmental Genetics and Population Genetics. The former is concerned primarily with laboratory oriented studies utilizing experimental animals whereas the latter deals with human studies at the population, family or clinical level. A major portion of the Branch program is devoted to study of the etiology and pathogenesis of oral facial malformation. The intent has been to develop a broad, integrated approach ranging from studies of basic embryology of facial development in lower animals to the identification of factors contributing to the production of facial defects in human populations.

An essential part of this approach involves the use of experimental animals with intrinsic susceptibility to facial malformations. Through a combined physiologic, anatomic, and genetic study of these defects, we attempt to define their developmental basis and identify contributing environmental factors. A further objective of animal studies is that of defining models of etiology and pathogenesis which have relevance to the human situation, and can be tested directly at the population or clinical level. Conversely, human studies are designed to produce leads which can be further elaborated and refined through animal experimentation. There is, at the moment, an abundance of potentially fruitful leads to be pursued in both human and animal studies.

The staff of the Branch includes four permanent investigators supplemented by one visiting fellow, one research associate and supporting personnel. Staff investigators have authored and co-authored nine articles which have appeared during the past year. Eight manuscripts are presently at the press and six more are pending review by various journals.

Although a relatively high level of productivity has been maintained, the increasing restriction of resources, particularly personnel, have severely limited our ability to implement the Branch program fully. For example, the strikingly successful application of interspecies grafting techniques, discussed in the report of the Developmental Genetics Section, has opened a variety of opportunities for studies of facial development which cannot now be fully exploited. Similarly, data is accumulating which suggests that both direct and modifying effects of genes on certain hormonal and nutritional aspects of maternal physiology are important determinants in abnormal development. Efforts are being made to follow up the most promising of these leads, either intramurally or through collaborative studies. However, additional personnel would greatly facilitate these efforts.

Because of the wide range of genetic, endocrine and environmental factors involved in the control of development, a broad genetic approach, able to follow leads through multidisciplinary collaboration, may yield the

most rapid progress toward the diagnosis and prevention of human craniofacial malformation.

Report of the Developmental Genetics Section
National Institute of Dental Research
Summary Statement

The two fundamental propositions on which the research of the Developmental Genetics Section is based are that the control of development is largely genetic, and, more specifically, that the general pattern of this control is common to all vertebrate species. From these propositions it follows that delineation of the mechanisms of hereditary abnormality of development in experimental animals is applicable to the interpretation of human malformation, which cannot be easily or directly studied. Because of this homology of the developmental process, inferences may be drawn about the human condition from experimental animals whether the primary abnormality is elicited by a defective gene or by an environmental teratogen.

Embryonic development in mammals falls under genetic control in two principal ways. Firstly, the instructions coded within the embryonic genome directly affect the proportions of developing parts by controlling both the growth rates of individual tissues as well as their ability to interact with each other to form organs. Secondly, the maternal genome has its own impact in influencing the nature of the fetal environment, as a consequence of maternally derived nutritional and hormonal substances which in their own right can affect development. Either or both aspects of genetic control may thus be involved in malformation.

The major focus of the Developmental Genetics Section is on the control of normal and abnormal development, particularly that of the face. Since cleft lip and palate are malformations in many mammals, this Section uses experimental animals as systems to determine the genetic and environmental factors that predispose to facial clefts.

Experimental embryology as a science and methodology is applied to the determination of the events and mechanisms of normal face and head development. Mutant, highly inbred strains of mice with cleft lip and palate or isolated cleft palate are utilized as models for the comparable defects observed in man. The inbred lines are tested for their differences in response to environmental teratogenic stimuli, and treatments are designed to enhance or inhibit the teratogenic responses. These are based on morphological, biochemical and hormonal differences found between the strains during development. When defined models become available, they are tested for application to man by the appropriate clinical and genetic methods.

Embryology of the Face

Progress in the determination of the events of facial development has been greatly enhanced during the last year by the application of interspecific grafting techniques between early chicken and quail embryos.[1] Because quail cells contain a self-replicating intranuclear chromatin mass,

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This report is based upon progress achieved during the year in Project Nos. NIDR-HG-001-(a)-(54), NIDR-HG-002-(a)-(62), NIDR-HG-003-(b)-(67), NIDR-HG-004-(b)-(70) and NIDR-HG-005-(a)-(72).

they can readily be identified in chick-quail transplants, and the cellular origins of differentiated tissues may thus be determined with accuracy never before possible.

Using this technique, the borders of the neural crest components of facial tissues have been specifically localized, and the primary role of neural crest-derived mesenchyme in the formation of the facial skeletal tissues has been confirmed and extended. Extrapolation of this information to man indicates that a number of facial malformations result primarily from defective crest cell development.[2] Use of the chomatin cell marker has helped to clarify a number of additional problems. For example, it has been determined that the supporting cells of cranial ganglia are of crest origin even in those ganglia where the neurons originate from placodes. It has also been demonstrated that neural crest cells contribute significantly to the anterior pituitary gland and there is evidence that cells of this origin may be responsible for the production of adrenocorticotrophic and melanocyte stimulating hormones.[3]

Cells have also been found to migrate from the rhombic lip portion of the neural fold into various regions of the brain including the region apparently homologous to the substantia nigra of mammals. The observation that high concentrations of adrenergic neurons are found in the substantia nigra[4] suggests that central as well as peripheral adrenergic neurons originate from neural fold cells.

Experimental Cleft Palate

The A/J mouse has a well documented sensitivity to the induction of isolated cleft palate in embryos of mothers treated with the adrenal steroid cortisone or synthetic glucocorticoids.[5] This inbred strain can also be induced to produce isolated cleft palate by an environmental "stress" such as shipping during pregnancy.[6] During the past year a simple stress system which regularly produces 40% isolated cleft palate in surviving embryos without drugs or surgical treatment has been developed to allow laboratory study of this type of cleft palate. Critically timed deprivation of drinking water in a low humidity environment are the "stress".

Because adrenal corticoids have been shown to be effective teratogens in mice we have developed a radioimmunoassay for corticosterone, the primary adrenal steroid of the mouse. Using this test we have shown that timed deprivation of drinking water and low humidity result in a more than twofold increase of corticosterone in the serum of A/J mice. Other experiments have shown that subcutaneous injection of corticosterone acetate in pregnant A/J mice can give up to 80% isolated cleft palate in the offspring.

Examination of embryos after water deprivation or corticosterone treatment shows that they are delayed in development and that there is hemorrhage from the embryonic yolk sac circulation. Embryos of C57BL/6 mice, which are relatively resistant to steroid induced isolated cleft palate, do not show the yolk sac hemorrhage or growth retardation after dehydration.

Preliminary observations have been made of differences in the proportions of the snout to those of the tongue in embryos of different strains of mice that vary in propensity to cleft palate. These proportions are considered to be of interest because the tongue must drop down into the floor of the oral cavity from between the palatal shelves for palate closure to occur. Thus a relatively large tongue or a relatively small oral cavity may impede the normal process of tongue clearance from between the shelves. Small snout is associated with increased risk of cleft palate in the data collected so far.

A mutant line of laboratory mice (oel) has been reported to have isolated cleft palate with open eye as a mendelian recessive trait.[7] We have found that cranioschisis occurs in 7% of the embryos of this line but not with cleft palate. The genetic and embryological interactions between these two traits involving the development of the head may indicate basic cell relationships in the development of the face and skull.

Future Plans

The proposed course of research in the Section builds on our past observations in animals and on suggestions from clinical studies of human malformation. Study of the details of the development of the face in birds utilizing the interspecific transplant technique will be continued in order to provide a rational basis for interpretation of genetic defects observed in man and experimental animals, and to provide a foundation for similar work in mammals as those techniques become possible. Experiments utilizing the isotope marker for tracing the migrations of crest cells in rat embryos developing in culture will be extended. Also, the possibility of utilizing scanning electron microscopy for identifying migrating avian and mammalian crest cells through their three-dimensional morphology is being explored.

Induction of isolated cleft palate in A/J mice by dehydration provides a standard test system which we plan to manipulate by changing the nature of environment and the genes involved in the stressed animals. The genome can be changed by crossing A/J with other inbred strains and the environment can be adjusted by laboratory methods. The effect of these changes can be observed on growth and occurrence of cleft palate in embryos and on yolk sac hemorrhage. The corticosterone assay system can be used to evaluate the hormone levels in the mother and fetus.

The analyses of homonal levels in relation to the risk of cleft formation or other malformation will be extended to include other adrenal hormones and thyroid hormone. Thyroid may be particularly significant because of its essential role in all metabolic processes, and because it has already been reported to be effective in reducing the incidence of cleft lip and palate in A strain mice, known to be predisposed to a high spontaneous rate.[8] Also, since inhibtion of thyroid release by elevated adrenal hormone levels is well documented, the possibility exists that the "stress" or adrenal hormone results obtained so far may be a function of thyroid action rather than being mediated directly by glucocorticoids or hemorrhage. The interaction of adrenal and thyroid in teratogenesis can be tested directly in a susceptible strain like A.

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Report of the Population Genetics Section
National Institute of Dental Research
Summary Statement

The primary focus of the Population Genetics Section throughout the past year has been on family and epidemiologic studies of congenital malformations. These include broad studies of outcome of pregnancy of American Indian populations, as well as studies relating specifically to oral facial malformations.

Congenital Malformations in American Indians

The relative frequency of congenital malformations in various population groups has received considerable attention. Of particular interest has been the comparison between races and the effects of interracial crossing on malformation experience. In studies of Japanese infants, Neel[1] observed that the total malformation rate was relatively constant between major racial groups, even though specific malformations varied considerably. For this and other reasons, he proposed that " . . . a significant fraction of human congenital defects . . . might be due to simultaneous homozygosity at many loci . . . ." In a study of racial crosses in Hawaii, Morton et al.[2] obtained similar results in regard to total malformation rate in different races. However, these data showed no effect of outcrossing and therefore . . . "no evidence that multiple homozygosis or phenodeviants are of importance in etiology of congenital defect." More recently, Carter[3] suggested that the total malformation rate among racial groups is not constant.

Our studies of the American Indian were designed to provide information on overall malformation rate as well as patterns of specific malformations for comparisons with other Mongoloid as well as Caucasoid population groups. In addition the data allow a comparison between the major linguistic stocks of the American Indian population as well as an evaluation of the effects of racial admixture in this particular group. For these studies, we have collected clinical records of approximately 45,000 births in Indian Health Service Hospitals.

There is a threefold variation in the frequency of total malformation rate among the major linguistic stocks. Considering that these groups are relatively similar genetically, and that the data are obtained from a single hospital system using the same records and common standards for reporting, it seems unlikely that the previous suggestions of a similar total malformation rate among different populations is valid. Specific malformations also show considerable difference between major linguistic groups. Three malformations, i.e., cleft lip and palate, clubfoot and polydactyly, show significant correlation between their frequency and the degree of Caucasian admixture. Thus as the degree of Caucasian admixture increases, the frequency of cleft lip and palate

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decreases. Clubfoot, by contrast, increases as Caucasian admixture increases. The relationships appear to be essentially linear, and can be interpreted as showing the effects of additive genes, although differences in environmental conditions could produce the same effect. Analytical models incorporating a variety of environmental variables are now being developed.

As predicted by the genetics of twinning and by data from other populations, the frequency of twins among the American Indians is positively correlated with the degree of Caucasian admixture in the mother but not in the father. This finding lends support to the validity of the data and their ability to detect genetic effects.

Facial Morphology in Relatives of Oral Cleft Patients

Another major activity of the Population Genetics Section involves studies of facial morphology in parents and co-twins of children with oral clefts. There is evidence in mice from studies by Trasler[4] suggesting that the size and shape of the facial processes are related to the embryo's susceptibility to cleft lip. Three relatively small studies in humans suggest that parents of children with oral clefts demonstrate alterations in facial morphology.[5, 6, 7] All of these studies are open to some question, on the basis either of the technical methodology or of the adequacy of control groups used.

In collaboration with the Lancaster Cleft Palate Clinic, we have obtained frontal and lateral cephalograms on parents from approximately 200 families with affected children. Similar data have been obtained on approximately 100 control families. The objectives of these studies are to utilize parameters of facial morphology in an attempt to define different subgroups of cleft families, and to determine if facial measurements can be useful for genetic counseling purposes. Facial morphology might have additional utility in elucidating etiologically different subgroups and high risk families which could be used for other studies.

Parents of children with clefts tend to be somewhat smaller in stature overall head size, and show some increase in interorbital dimensions. Shortening of the mid-facial area and, perhaps, some differences in size and shape of the mandible are also seen. Because there are likely to be socio-economic and ethnic differences confounding these results, as well as etiologic heterogeneity, we feel they should be considered tentative until additional data are obtained.

Another aspect of the study involves the use of discordant monozygotic twins. Because of their identical genetic makeup and similar environment in the uterus, we expect identical twins to offer the best opportunity for definition of genetically based facial characteristics relating to susceptibility to cleft lip and palate. By hypothesis, the unaffected identical co-twin of a child with cleft lip or palate will show many of the predisposing facial characteristics contributing to production of a cleft, even though the child himself does not have a frank cleft. At this time, we have about 20 cases which can be used and we are continuing

to contact various treatment centers in hope that we may substantially increase the sample.

During the past year, Dr. MacLean, of this Section in collaboration with Dr. Newton Morton (University of Hawaii) has been involved in studies of segregation analysis of complex traits. These studies have direct application for the estimate of recurrence risks in families with oral clefts and may ultimately be important in developing tests for alternative models of etiology. A result of Dr. MacLean's work has been the development of a method for establishing recurrence risks in families where only remote relatives are affected.

Future Plans

The Section will continue to be involved in the studies described. In the case of the American Indian Newborn Study, no new data is being collected, but analyses will continue. In the studies of facial morphology we plan to continue to add to our data base, which is approaching sufficient size to allow meaningful statistical analysis.

Plans are being formulated with Dr. W. Wertelecki (University of South Carolina) to initiate a study on the possible role of dilantin in the production of human cleft lip and palate. Several earlier reports[8, 9, 10] had suggested an association between ingestion of dilantin in the first trimester and birth of children with oral clefts. Recently, a prospective epidemiologic study[11] has more convincingly shown this association. Other studies[12] have shown that anticonvulsant drugs lower serum folic acid levels. Folic acid antagonists, e.g., Methotrexate, are known to produce malformations and abortions.[13, 14] There are also suggestions of reduction in the recurrence rate of clefts among mothers on vitamin supplementation, including folic acid, after the birth of one affected child.[15, 16] If the association can be definitely confirmed it will introduce an area of maternal metabolism which will merit careful scrutiny.

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SUMMARY REPORT OF THE LABORATORY OF BIOCHEMISTRY

The research efforts of the laboratory the past year have been directed toward three major biochemical problems: connective tissue chemistry and metabolism, the action of a group of enzymes called transglutaminases, and the control of growth and differentiated functions in mammalian cells at the nucleic acid level. It is of considerable interest that in each case the program covers a broad scope all the way from studies at the molecular level to biological problems with important medical and dental implications. This is in keeping with the emphasis in recent years on relevance.

The program on connective tissue continues to concentrate on collagen, the major structural component. The Protein Chemistry Section emphasizes structural and chemical studies while the Connective Tissue Section is more biologically oriented. The day-to-day collaboration between basic scientists and clinically-oriented physicians in the same laboratory has worked well and promises to continue to be productive.

The orientation of the program of the Cell Biology Section begins at the level of man and the mammalian cell, but as their program has developed they have found an increasing need to ask questions at the molecular level, a trend that is not unusual. This is evidenced by a new study on proteins associated with ribosomes and a new study on tRNAs and mRNA in collagen biosynthesis. The primary interest of the latter study is on translation. Collagen biosynthesis is a useful model, but the results will of course be of interest to the connective tissue group.

The program of the Enzyme Chemistry Section is basically chemical. However, it has evolved from an interest in enzyme catalysis largely isolated from biological problems to one where the biology is becoming increasingly important. This has happened as it has been shown that the enzyme transglutaminase, chosen largely as a matter of convenience, has at least two major physiological roles, the cross-linking of fibrin and the cross-linking of hair proteins through $\varepsilon(\gamma\text{-glutamyl})$-lysine bonds. It is likely that other major roles will be found for the enzyme. Ramifications extend in many directions and even overlap the interests of the Connective Tissue Section where cross-links of another type involving lysine-derived aldehydes are being studied.

In several of the programs in the laboratory, collaboration with outside laboratories has become an important feature. In two cases, the University of Washington Medical School and the Hadassah School of Dental Medicine, joint projects are supported by contracts. Active collaborative projects also exist with the Polymer Division, National Bureau of Standards; the Dental Institute, University of Michigan; the Dermatology Branch, NCI; the Gerontology Branch, NICHHD; the Department of Genetics, Johns Hopkins Medical School; the Chemistry Branch, NCI; and the Dept. of Microbiology, Georgetown University. There is also active interaction with other NIDR programs, particularly the Laboratory of Microbiology in the immunological and inflammatory disease areas.

During the past year the administrative organization of the laboratory has remained essentially unchanged. One senior scientist left to become a Professor of Biochemistry at a Medical School. However, he is not completely

lost to us as he is associated with a Dental Institute and will maintain close ties. This is another example of the many instances where this laboratory has provided the training ground for an investigator who has gone on to bigger and better things.

At this writing the laboratory has 24 investigators about equally divided between MDs and PhDs in its four sections. Of these, six are permanent employees and eighteen are Staff Fellows, Research Associates or Guest Workers. The last category, in which there are seven investigators, constitutes an important group of talent supported by funds outside the intramural program. The research program of the laboratory is also highly dependent upon a skilled and dedicated group of persons, presently sixteen in number, in various supporting positions.

By chance, a larger-than-usual proportion of investigators in temporary positions completed their assignment early in the year. These have now all been replaced and a few more added for a total of ten new investigators. This has resulted in a considerable reorganization of laboratories and the initiation of some new projects. These are described in the Section reports. Perhaps the major material addition has been the purchase and installation of an automatic amino acid sequencer and accessory equipment.

The use of NIDR and central NIH computer facilities in the programs of the laboratory continues to increase. After a long and frustrating developmental period, it now appears that automatic data collection and calculation for amino acid analysis will soon become routine. Computer facilities are being used routinely in association with radioactive counting, enzyme kinetics and analysis of amino acid sequence data.

Two laboratory seminar series have provided an opportunity for scientific and social interchange among laboratory members and a means of keeping abreast of active research areas of particular relevance to laboratory programs. One is the usual "journal club" twice-weekly type where investigators can report on their own work or on results of special interest from current literature. The other is a once-monthly series in the connective tissue field where investigators from other laboratories present an informal seminar primarily for members of this laboratory. It is followed by a social hour including spouses which provides an opportunity for all to get to know one another. Both series have been well attended and have served their purposes well.

One measure of productivity is publication rate. During the year May 1, 1971 to May 1, 1972, 22 publications (not including abstracts) authored or co-authored by members of this laboratory were cleared through the Institute editorial procedure. Of these, three were chapters in books and the rest were manuscripts for publication in scientific journals. This is a very respectable record particularly considering the many new investigators and new projects starting this year.

SUMMARY REPORT OF THE CELL BIOLOGY SECTION*

Background

The genetic information stored in DNA is ultimately translated into the physiological activity of differentiated animal cells and tissues. Studies in progress in the Cell Biology section are aimed at elucidating some of the biochemical processes by which this translation is achieved and controlled.

The work of the section is divided among three major aspects of this problem:

1. How are alterations in the differentiated state of the cell correlated with changes in the synthesis and processing of various classes of RNA, the primary intermediate in the translation of genetic information? What biochemical processes regulate such changes?

2. How is the differentiated state of the cell determined by the activity and organization of the protein synthesizing mechanism of the cell and how are these factors controlled?

3. How do different cells interact with one another and with their milieu so as to produce the coordinated behavior characteristic of differentiated tissues?

Progress

1. For several years, the RNA metabolism of human peripheral lymphocytes has been under investigation. This cell offers certain notable opportunities for research: the physiological activity of this cell *in vivo* includes prolonged periods of non-growth, followed by abrupt onset of growth in response to an immunologic stimulus. This sequence may be studied *in vitro* (1). The capacity to vary its growth rate in response to external stimuli may be viewed as an aspect of the differentiated function of the lymphocyte. An understanding of the biochemical mechanisms which control the growth of lymphocytes *in vitro* will then bear on two major problems in modern biology and medicine: the control of cell growth *per se*, and the regulation of cell differentiation. Moreover, knowledge in this area will extend our understanding of problems in immunology.

Previous studies in this section have established the patterns of RNA metabolism characteristic of normal resting and growing lymphocytes (reviewed recently (1,2)). In the course of these studies, alterations in RNA metabolism characteristic of the shift from the resting to the growing state have been identified (3,4). In particular, a previously undescribed mechanism of cell growth regulation, based upon the control of degradation of newly-form-

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* This report is based upon progress achieved during the year in Project Nos. NIDR-LB-72-401-(b)-62, NIDR-LB-72-402-(b)-67, NIDR-LB-72-403-(b)-69, NIDR-LB-72-404-(b)-72, and NIDR-LB-72-405-(b)-72.

ed ribosomal RNA, was reported (5). The growth of resting lymphocytes is restricted by a process which limits the rate at which new ribosomal RNA can be accumulated. RNA molecules synthesized in excess of this limited amount are degraded. Such "wastage" may affect more than half of the newly synthesized ribosomal RNA molecules in resting lymphocytes. That control of such wastage may be important in cell growth regulation is shown by the rapid reversal of such wastage following the onset of lymphocyte growth (6, 8).

Evidence has now been obtained which shows that the survival of newly synthesized ribosomal RNA molecules is dependent on the availability of proteins ("ribosomal protective proteins") which appear to protect the RNA from degradation (7,8). The number of such protein molecules available at any moment will determine the number of ribosomal RNA molecules which are protected; the remainder are degraded. Since normal cell growth is dependent on the accumulation of new ribosomes, the rate of synthesis of the ribosomal protective protein may constitute a major cell growth regulating process.

We propose that ribosomal protective protein is one of the large complement of proteins which are components of the ribosome. A major effort is in progress to isolate, characterize and purify this protein. This is being done coordinately in lymphocytes and in HeLa cells, the latter being used as a source of large quantities of material for study. To date, ribosomes from normal growing lymphocytes and from HeLa cells have been isolated, their proteins separated and analyzed by acrylamide gel electrophoresis. Examination of the relative rates of synthesis of the various ribosomal proteins in rapidly growing lymphocytes is currently in progress in an effort to localize components of this complex system which may be produced at limiting rates. Results to date indicate that particular proteins show the rapid labeling expected of a ribosomal protein whose production is rate limiting for ribosome assembly.

Future progress of these studies will involve large-scale preparation of ribosomes and ribosomal subunits; detachment and analysis of ribosomal proteins for activity in protecting RNA against nuclease; measurement of growth-related changes in production of such protective proteins in lymphocytes.

In addition, studies relating to the regulation of synthesis of ribosomal and other RNAs in resting and growing lymphocytes are in progress. These, it is anticipated, will shed light on the general problem of the regulation of genetic activity in animal cells.

To aid in these studies, a computerized approach to the analysis of the kinetics of RNA precursor pool labeling by radioactive materials was developed and applied to the study of RNA labeling in lymphocytes. This method permits the investigator to correct RNA labeling data for changes in precursor pool specific activity without the necessity for measuring the pool specific activity directly. For work with lymphocytes, this is essential, both because it was shown that slow labeling of RNA precursor pools markedly influences the labeling of RNA, and because the amounts of lymphocyte material available are too limited to permit direct precursor pool quantitation.

In a related study, a unique ribonuclease, widely present in animal tissues and fluids, was discovered by Dr. Stern in this laboratory (10). It has been further studied, with the following results:

A. Molecular weight: 40-45,000 Daltons.

B. Slightly basic, co-electrophoresing with γ-globulin.

C. Specific for pyrimidine sequences of double stranded RNA only.

D. Elaborated primarily by the reticulo-endothelial system (macrophages).

E. Associated with the polysome fraction of the cell.

This enzyme has been shown to cause anomalous production of interferon in mice injected with poly I.C. (11).

A collaborative study is under way with the Dept. of Microbiology, Georgetown University, to determine whether this enzyme plays a role in the replication of viruses which may have a double-stranded stage in the replication of their RNA.

2. Differentiated animal cell systems are often characterized by the production of large amounts of specific proteins. Such production varies not only among different tissues, but also during various stages of development of particular tissues. The means by which such differentiated states of protein synthesis are determined and maintained is being sought at the biochemical level by an analysis of the protein synthesizing elements in a cell-free system.

During the past year, cell-free protein synthesizing systems have been set up using rabbit reticulocytes and Krebs ascites tumor cells as sources of ribosomes and required factors. These systems have been and will be used to translate various added messenger RNAs into proteins: hemoglobin mRNA; polyuridylic acid; certain viral RNAs. Work is in progress to isolate and purify the messenger RNA of collagen for translation in this system. The large amount of information about the structure of collagen which has been accumulated by other Sections in the Laboratory of Biochemistry will prove invaluable in this aspect of the problem. Achievement of this goal will also provide fuller knowledge of the structure (amino acid sequence) of the collagen molecule and may clarify certain questions relating to the control of collagen production.

The current source for collagen mRNA is the chick embryo calvarium. This tissue devotes up to 60% of its protein synthetic activity to collagen production. A major question is whether this emphasis is based upon the proportion of mRNA devoted to collagen, or upon the extensive utilization of a small amount of mRNA.

Evidence for the former possibility is being sought through attempts to label

and isolate the collagen mRNA and mRNA-bearing particles from developing chick calvaria. The second possibility is being investigated in terms of the enzymes and transfer RNA molecules which are essential to the translation of the collagen mRNA. The unique amino acid composition of collagen (high glycine and proline content) suggests that tissues active in the production of collagen may be enriched in the amino acylating enzymes and/or isoacceptor tRNAs required for those amino acids. tRNA preparations have been isolated from chick calvaria and from liver as a control. A procedure has been developed for the separation of isoacceptor tRNAs for proline, glycine and arginine in order to determine whether enrichment for collagen-related amino acid isoacceptors is present. Initial studies in this determination have already been carried out and suggest that such enrichment may occur.

Other aspects of the interrelationship between the synthesis of particular proteins and variations in cell growth are being studied.

In collaboration with the Chemistry Branch, NCI, the determination of the enzyme, aryl hydrocarbon hydroxylase, in lymphocytes was performed.

This enzyme is induced in cells exposed to various carcinogenic hydrocarbons, and is apparently part of the organism's mode of metabolizing such materials. The ready availability of lymphocytes suggested these cells as a source for the study of this enzyme in human subjects with neoplasms or positive family histories. In this preliminary study it was found that:

a. Resting lymphocytes have low levels of this enzyme, but may be induced to show its activity by incubation with an appropriate hydrocarbon.

b. Growth stimulation raises the baseline level of enzyme present, and increases the magnitude of the rise in response to hydrocarbons.

C. The enzyme is known to be associated with the endoplasmic reticulum in other cell systems. It showed significantly greater hydrocarbon inducibility in lymphocytes exposed to growth-stimulating agents (poke weed mitogen) which are known to stimulate endoplasmic reticulum production. This result confirms the association of the enzyme with endoplasmic reticulum in lymphocytes as in other tissues.

3. The lymphocyte system provides a model for the study of interactions between cells in the production of differentiated cellular activity. This is an area of profound ignorance in modern biology.

When lymphocytes are incubated with specific antigens to which the cell donors have been immunized, cell growth is induced. This response requires the participation of another cell type, the macrophage. It was found that the macrophage interacts with the antigen so as to render it stimulatory to the lymphocyte. This requires active metabolic processes by the macrophage but does not require immunological sensitization of that cell. Immunological specificity for the response resides with the lymphocyte (9).

The subcellular steps in the processing of antigen by macrophages have been studied. In summary, antigen is rapidly ingested by macrophages through endocytosis. Although most of the ingested antigen is degraded, small amounts of retained antigen are bound to subcellular components. One of these may be an antigen-membrane-ribosome complex which may play a role in enhancing the immunogenicity of the antigen for lymphocytes. The immunogenicity of this and other subcellular components is presently under study. It is hoped, ultimately, to clarify the precise mode of interaction between the lymphocyte and the macrophage in presenting the processed antigen to the lymphocyte so as to evoke a growth response.

These studies have involved extensive cooperation with the Immunology Section, Laboratory of Microbiology, NIDR.

Significance

The problems under investigation by the Cell Biology section are important both from the viewpoint of basic research in cellular biochemistry, and in the broad attack on the important practical problems of neoplasia, growth and differentiation, and immunological disease. In these latter areas, the studies outlined are designed to provide the basis of understanding of normal regulatory mechanisms which is necessary for a rational approach to disease states in which such mechanisms may be distorted. For example, the current massive effort to find and prove a viral etiology for cancer will prove of small benefit to the public if the means by which such putative viruses influence normal cellular regulatory processes remains unknown. Without an understanding of those normal processes, the nature of disorders affecting them cannot be fully comprehended.

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SUMMARY REPORT OF THE CONNECTIVE TISSUE SECTION*

Background

Much has been learned about the nature of the collagen molecule and the manner in which it is packed and cross-linked to form strong fibers. However, it has not been clear how chain composition in the molecule is established, why macromolecular assembly occurs rapidly nor how secretion and fiber formation take place. Recent studies from this (1,2) and other laboratories (3,4) have identified precursors of collagen which may carry out these early functions. Isotope studies show that polypeptides (pro α chain) 10-20% larger than α chains are formed first, assembled into a macromolecule (procollagen) and only later converted to collagen. Brief treatment with a protease will convert the precursor to collagen-like molecules, suggesting that it contains extra peptidyl material. A major effort of the section is directed toward the isolation and characterization of procollagen and the elucidation of its conversion to collagen.

Numerous human diseases appear to involve changes in the synthesis or degradation of connective tissue components. We have been interested in investigating such diseases, including certain rare inherited disorders believed to involve collagen, as well as inflammatory conditions wherein collagen is secondarily involved. Inherited disorders of collagen are particularly suitable for observation because they may be studied *in vitro* using fibroblasts cultured from affected individuals.

A well recognized phenomenon in infections and in inflammation is the accumulation of polymorphonuclear (PMN) leucocytes at the site. It is generally thought that these cells are attracted to the area by a chemical gradient in a process termed chemotaxis. Similar migrations can be induced *in vitro* in response to chemotactic substances produced by a variety of bacteria and to certain substances produced when the host's effector systems are activated. We have been studying a material produced by *E. coli* and C5A, a substance produced during the activation of the complement cascade, both of which attract PMN leucocytes *in vitro*. We hope to define the nature of these substances and the reaction in the cell which induces directed migration.

Progress

With the exception of an inherited disorder in calves (dermatosparaxis) where procollagen-like molecules accumulate, isotopic techniques have been required to demonstrate the precursors. Apparently the pool of precursor molecules is small and collagen is not readily separable, thereby hampering chemical characterization. Recently, we have developed methods to prepare procollagen, free of collagen, in sufficient quantity to begin characterization. Amino acid analyses indicate that procollagen is more acidic than collagen, has a lower glycine content and contains cysteine. Procollagen is

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* This report is based upon progress achieved during the year in Project Nos. NIDR-LB-72-201-(b)-62 and NIDR-LB-72-202-(b)-61.

chromatographically distinct from the dermatosparaxic calf collagen mentioned above, which may indicate partial conversion in the diseased material. Fibroblasts in culture produce quantities of procollagen which contain components of still greater size than the pro α chains. When treated with an agent that specifically cleaves disulfide bonds, pro α chains are formed. It is possible that disulfide bond formation between pro α chains is a normal and essential reaction in the formation of the procollagen molecule. If true, such bonds must be rapidly cleaved, since the procollagen labeled after a brief pulse is readily separated into pro α chains by denaturation alone.

The nature of the collagen produced by cells obtained by amniocentesis is being examined. These cells produce a collagen with little of the α2 chain and a low concentration of hydroxyproline, suggesting a decreased hydroxylation of proline. It may be possible in the future to identify affected carriers of collagen defects in utero to assist in genetic counselling. The first such defect in man has recently been identified (5). The collagen in the skin and bone of these patients lacks hydroxylysine and the enzyme, lysine hydroxylase, that forms the amino acid is present in low amounts. We are studying another kindred with this disorder in cooperation with the Genetics Department at the Johns Hopkins University. Other patients under study have the same general appearance but normal amounts of hydroxylysine. By studying these rare disorders of connective tissue we expect to identify as yet unknown steps in collagen metabolism.

The essential role of collagen cross-linking in the normal development of connective tissues has been one of our continuing interests (6,7). Recently, we have been studying certain strains of mice which develop dissecting aneurysms of the aorta. We find evidence of defective cross-linking of their skin collagen. A similar defect in the aorta may explain its weakness. It is possible that these mice may provide a useful model of defects occurring in blood vessels in man.

We are also studying the reactions relevant to the removal of collagen from bone and other tissues (8). The studies of colleagues in the Laboratory of Microbiology and Immunology, NIDR, as well as others, have identified a variety of host effector systems to be active in inflamed tissue. A portion of fifth component of complement is cleaved in inflammation and attracts polymorphonuclear (PMN) cells to the area by chemotaxis. Previous work in this Institute (9) has established that PMN cells contain collagenase in granules. We have found that antigen-antibody complexes cause the spillage of collagenase from these cells. In addition, lymphocytes, stimulated by specific antigens to which they are sensitive, secrete a substance that induces bone to resorb (10). This may explain the bone loss observed near chronically inflamed tissue in periodontal disease.

The manner in which certain inflammatory cells are attracted to infected or inflamed areas is under study. The chemotactic complement fraction, C5A, elicits a highly reproducible migration across filters in test chambers. Chromatographic purification is under way. The bacteria produce more than one chemotactic substance. Their isolation has been hampered by assaying difficulties. However, results so far indicate that one fraction contains hypoxanthine, as indicated by its mass spectrometric, chromatographic and

ultraviolet absorption properties. Media used to culture E. coli contain another more potent product with a molecular weight of less than 2000 which is inactivated by pronase.

Significance

While connective tissues were once considered to be metabolically inactive, it is now known that synthetic and degradative processes in these tissues undergo marked alterations in response to physiological stimulus and disease processes. We have attempted first to understand the steps in the formation and development of the major structural components of connective and second, to apply this information to diseases affecting these tissues. Particular attention has been directed to experimental disorders, since these offer the best opportunity to understand basic mechanisms which may be operative in human diseases. Sufficient information has been obtained to encourage the study of inherited and acquired disorders of connective tissues in humans.

The directed migration of cells is a general biological response which is important in development, host resistance and repair. Methods used to study the chemotaxis of PMN leucocytes may be applicable to other cell types and be essential to the understanding of a variety of cellular reactions.

Future Plans

We expect to continue to investigate the biochemical steps involved in the formation and destruction of connective tissues. At present we believe that the study of procollagen and its conversion to collagen offers the possibility to understand and control fibrosis. The interactions of various tissues both humoral and direct are definitely involved in the development and degeneration of connective tissues. Experiments designed to clarify these interactions are under consideration. Collaborative efforts are being sought to apply recent developments in other research areas to our area.

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SUMMARY REPORT OF THE ENZYME CHEMISTRY SECTION*

Background

Studies carried out during the last two years have been directed toward characterization of enzymes, termed transglutaminases, that are responsible for the formation of γ-glutamyl amide bonds in proteins and polypeptides. These enzymes catalyze transfer reactions at the carboxamide group of peptide-bound L-glutamine with a high degree of stereospecificity (for review see (1)). In the presence of acceptor amines, the transfer reaction results in the formation of substituted amides ($-CONH_2 + RNH_2 \rightarrow CONHR + NH_3$).

One of the well-characterized covalent cross-links between and within protein molecules is the ε(γ-glutamyl)lysine bond. There has been increasing evidence of occurrence of this bond in various proteins, e.g. insoluble fibrin clots, L-cell membrane, native wool keratin, and citrullin-containing protein fraction of hair (for review see (1)). The wide occurrence and obvious importance of γ-glutamyl amide bonds has led us to focus attention on the enzymes responsible for their formation.

Progress

Results obtained during the past year serve to define three distinct groups of transglutaminases in mammals (2). Studies carried out using guinea pig and human tissues show that these groups of transglutaminases may be distinguished on the basis of their physical, chemical, immunological and enzymatic properties. These groups are, a) the tissue enzyme found in liver, spleen, adrenal gland, kidney, muscle and other organs. Liver was found to possess the highest activity in guinea pigs whereas the lung shows the highest activity in humans. Red blood cells from both humans and guinea pigs contain a transglutaminase that is indistinguishable from that of hepatic tissue; b) protransglutaminases (blood coagulation Factor XIII) have been localized in blood plasma and platelets and in uterus and placenta (2,3,4). The plasma zymogen of molecular weight 320,000 was found to be composed of two each of two different subunits. The protransglutaminases of platelets, placenta and uterus, however, were observed to contain only one polypeptide chain of molecular weight 80,000 (2). Each is activated by thrombin with a concurrent loss in molecular weight of about 4,000. Further, the proenzymes may be activated by prolonged storage at 4°. This activation results with no change in molecular weight; c) two transglutaminases are found in homogenates of the inner root sheath of the guinea pig hair follicles (5). One is indistinguishable from the hepatic enzyme, but the other which is present in greater quantity, has not been detected in other organs or tissues. The native hair follicle enzyme of molecular weight 54,000 is composed of two subunits of the same molecular weight.

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* This report is based upon progress achieved during the year in Project Nos. NIDR-LB-72-301-(b)-72, NIDR-LB-72-302-(b)-52.

Specificity and kinetic studies show that each transglutaminase catalyzes the formation of γ-glutamyl amide bonds by way of a common acyl transfer mechanism (6). Each enzyme causes formation of insoluble-fibrin, but each group of enzymes shows a different pattern of fibrin polymerization (2).

Binding studies of transglutaminases with plasma proteins show that only fibrinogen forms a tight complex with liver transglutaminase (2,7). The plasma zymogen does not bind to fibrinogen. An *in vivo* study with ^{14}C-labeled liver transglutaminase indicates that the fibrinogen-transglutaminase complex is cleared from plasma rapidly. Most of the label that is cleared from plasma is found in the liver.

Several approaches were taken in an effort to gain knowledge about the shape, structure and environment of the active site area of liver transglutaminase. These include "reporter"-group labeling of the enzyme active site (8) and kinetic studies on modified-peptide substrates and substrate analogs (9).

The "reporter" group studies involve the synthesis of a novel series of substrate analogs, compounds that contain a nitrophenol chromophoric group and a halomethyl ketone group within a molecule having a gross structure resembling substrate. Alkylation of the enzyme active site -SH residue by these compounds, followed by spectral examination of the resulting inactivated enzyme, revealed the hydrophobic nature of the active site in the presence of calcium ions. In contrast, in the absence of Ca^{+2}, the active site residue was found to reside in a more hydrophilic environment.

Kinetic studies using peptide substrates that are analogs of normal glutamine substrates have been aimed at a better understanding of the structural features necessary for substrate activity. These studies involved the synthesis of peptides containing unusual structural features. Kinetic analyses of glutamine peptides that contain various amide-related groups in the ω-acyl portion of the molecule indicate that a peptide derivative directly related to glutamine in gross structure can function as a substrate irrespective of the functionality at the ω-acyl portion of the molecule. However, these substrates function with drastically reduced efficiency as compared with glutamine substrates.

To investigate the importance of the amino masking group in model glutamine peptides, a series of blocked peptides have been prepared containing various amino-blocking groups (X-GlnGly). The results show that the enzyme has a kinetic preference for substrates containing hydrophobic groups in this position. This may indicate the existence of a hydrophobic binding site in the enzyme for the residue preceding glutamine in peptide substrates.

The discovery of enzyme-catalyzed transfer activity toward aliphatic amide substrates was unexpected. The aliphatic amides appear to function as substrates for transglutaminase by mimicking the aliphatic carboxamide side chain of glutamine. Kinetic studies on a series of aliphatic amides of varying chain length and degree of branching has revealed much about the shape and size of the enzyme active site. The study indicates that the active site -SH group in liver transglutaminase lies at the nadir or apex of a narrow cleft in which the aliphatic side chain of these substrates (and

presumably the side chain of glutamine) binds. The cleft appears to have specific dimensions which have been defined in terms of substrate side chain length.

Significance

A comprehensive study of various transglutaminases has shown that the enzymes are widely distributed in various organs and tissues, and that they may all be involved in the formation of ε(γ-glutamyl)lysine cross-links within and between protein molecules. These linkages are essential in maintaining the permanent rigid structure of many protein molecules.

The physiological importance of the protransglutaminases of plasma and platelets is well known. The finding of protransglutaminases in placenta and uterus indicates another regulatory control site of the blood coagulation process. Estrogen and progestrone regulation of transglutaminase levels in rabbit uterus has been observed (10).

The localization of a specific transglutaminase in hair follicles suggests a role of this enzyme in the formation of cross-bonding of the inner root sheath protein of hair.

During tissue injury or hemolytic disease, tissue transglutaminase may be released into plasma and could sustain physiological damage by causing intravascular coagulation or thrombosis. The binding by fibrinogen of tissue and red blood cell transglutaminases suggests a unique and hitherto unrecognized role of fibrinogen as a detoxifying agent, a role similar to that played by immunoglobulins.

The minimal substrate structural requirements for liver transglutaminase have been defined over the past year through the studies described above. We now have a better understanding of the mechanism of enzyme-substrate interactions in transglutaminase-catalyzed reactions. The technique of active site mapping, using straight and branched chain substrate analogs, is one which may be applicable to other enzymes and most certainly will be applied to studies with other transglutaminases. The "reporter" group studies have supplied valuable information about the active center of liver transglutaminase. The chromaphoric substrate analogs will be used for active site studies on other transglutaminases.

Future plans

To understand the function of human red blood cell transglutaminase, efforts will be made to isolate the enzyme and examine its enzymatic properties.

Detailed studies of protranglutaminases of plasma, platelets and other tissues will be made with special emphasis on the nature of the active sites, subunit compositions, and activation processes.

Further studies of the hair follicle enzyme are underway. Special attention is focused on the role of this enzyme in the normal metabolism of hard tissues, especially keratins.

The possible use of liver transglutaminase in localizing and determining the the orientation of membrane proteins and other structural proteins is under investigation.

Preliminary studies suggest a primary role for transglutaminase in wound healing. Attention will be focused on the possible interaction between fibrinogen and collagen as catalyzed by transglutaminase and the possible relationship of this interaction to wound healing.

Complete kinetic investigations will be carried out on the recently discovered liver transglutaminase activity toward aliphatic esters of glutamyl peptides.

Studies of the effect of various amino blocking groups on the reactivity of model peptide substrates will be continued. The effect of various metal ions on these activities of transglutaminase will be investigated.

There are plans to expand the substrate specificity studies described to some of the other transglutaminases currently under investigation in this laboratory.

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SUMMARY REPORT OF THE PROTEIN CHEMISTRY SECTION*

Background

Collagen is the major structural protein of all vertebrate and many invertebrate species. It is found not only in the major connective tissues, skin, tendon, bone and cartilage, but is an important component of tissues such as basement membranes, cornea and major blood vessels. The basic structure common to all or most collagens is a rod-like molecule about 3000 x 15A composed of three polypeptide chains of about 1000 amino acids each (95,000 molecular weight). Each chain is helical throughout most of its lengths and the three chains are coiled together in a major helix. The major interstitial collagens contain two kinds of chains (two α1 and one α2) but other collagens have identical chains.

Superimposed on this basic structure are variations inherent in the structural genes or added during the biosynthetic steps following translation. These include differences in amino acid sequence, degree of hydroxylation of proline and lysine, amount of attached carbohydrate, proteolytic alterations at the ends of the chains, amount and location of lysine- and hydroxylysine-derived aldehyde, and (in the fibril) the type and degree of covalent cross-linking. These and other aspects of collagen chemistry and structure have been recently reviewed (1).

Certain aspects of the broad problem are presently being emphasized in the program of the section.

These include: 1. Sequencing of cyanogen bromide peptides from collagen to provide comparative data and for correlation with structural studies. 2. The isolation of peptides with cross-links and determination of the positions of the cross-links in the sequence. 3. Species and tissue comparative studies on collagen chemistry. 4. The isolation and characterization of non-hydroxylated collagen to determine the role of the hydroxy group of hydroxyproline in collagen structure. 5. Biosynthetic studies on the rate of translation of collagen mRNA. 6. The role of the amino-terminal, non-helical regions of the α chains in the specific alignment of molecules in the fibril. 7. Cross-linking of collagen in implants. 8. A nuclear magnetic resonance study of collagen structure. 9. A similar NMR study on elastin.

Progress

Amino acid sequencing has been done under contract (#69-2230) with the University of Washington Medical School, Seattle, for nearly three years. The sequencing of α1-CB8, a cyanogen bromide peptide of 259 amino acid residues from rat skin collagen is now essentially complete (2-4). Similar studies will in the future be done in the section. A laboratory equipped with a sequencer is presently being established for this purpose.

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* This report is based upon progress achieved during the year in Project No. NIDR-LB-72-101-52 and NIDR-LB-72-102-62.

One purpose of the sequencing facility will be to locate the amino acid residues involved in intermolecular cross-linking. It is known from earlier studies that lysyl and hydroxylysyl residues near the amino- and carboxyl-termini of the α1 and α2 chains of collagen are involved in cross-linking after conversion to aldehydes. To find the other side of the cross-links, double-chain peptides containing cross-links are being isolated. By comparison with the peptides from soluble collagen not containing cross-links, the exact residues involved can be determined. One double-chain peptide has been obtained from a cartilage-specific collagen (5). However, this collagen is not as yet well enough characterized to complete the localization.

The cartilage-specific collagen (6) is the first well-documented example of a tissue-specific collagen that arises from a structural gene or genes different from those utilized for the major collagen common to skin, tendon and bone. Evidence for a minor collagen in human skin that is genetically distinct has also been obtained (7). It is likely that a wide variety of different collagens suited to different purposes will eventually be identified in higher animals. Knowledge of the major collagen of vertebrate skin has been extended by characterizing this collagen from human and baboon (8).

One of the unusual features of collagen is the presence of hydroxyproline. The role of this hydroxylated amino acid, however, is not understood. To determine this, collagen is being isolated from systems where hydroxylation has been inhibited. The physical chemical properties of nonhydroxylated collagen will be compared to those of collagen. Since a system that makes this material in large quantities has had to be developed, what is hoped will be a physical chemical study is presently a biosynthetic study closely associated with studies on procollagen in the Connective Tissue Section.

Another aspect of collagen biosynthesis that has been studied is the translation rate of collagen mRNA. A kinetic study (9) has demonstrated that the messenger for a pro α chain is translated at about 200 amino acid residues per minute. The α1 and α2 chains are synthesized simultaneously. It was also concluded that hydroxylation and helix formation probably occur while the α chains are still being translated and is complete very soon thereafter.

Although collagen is largely helical in conformation, it contains regions at the amino- and carboxyl-termini that have a different type of chemistry. These regions have special properties and perform special functions, the best established of which is that of serving as a site of cross-link formation. There is also indirect evidence that these regions may play an important role in the specific interactions that are involved in fibrillogenesis, the details of which are now being studied in an *in vitro* system where rates of aggregation can be followed. Peptides containing the amino-terminal regions are being isolated and their effect on the system is being determined.

Cross-linking of collagen *in vivo* is being studied at the Hadassah School of Dental Medicine under a PL 480 agreement (No. 06-041-1, Amendment 2) as an extension of the laboratory program. Purified collagen of various types when implanted in special chambers in experimental animals will continue to cross-link. The process can be followed easily since the implants can be readily

removed and analyzed. In the most recent studies it was found that cross-linking is markedly inhibited in hypophysectomized rats. Since the inhibition was observed with collagen low in aldehyde content but not with collagen high in aldehyde content, the effect seems to be on the enzyme that makes aldehyde, lysyl oxidase. The pituitary hormones appear to play an important role in the regulation of cross-linking.

Although the helical structure of collagen is quite well understood in outline, details of the factors that enter into molecular stability have long been argued. Nuclear magnetic resonance provides a new approach to this problem since it is sensitive to restrictions on the movement of atoms (protons or carbon atoms) and can therefore determine the state of certain functional groups in collagen in the native and denatured state. Preliminary proton magnetic resonance studies on the native and denatured states of α1-CB2, a well-characterized peptide of 36 residues from collagen, suggest that side chain interactions as well as backbone interactions may be involved in stabilizing the molecular structure.

Similar studies on elastin structure utilizing carbon magnetic resonance have been initiated. It is hoped that they will lead to a better understanding of the mechanism of elasticity in elastin. This study as well as the study on α1-CB2 are collaborative studies with the Polymer Division, National Bureau of Standards.

Significance

Since the biological role of collagen is largely structural, a knowledge of its structure is necessary to an understanding of its function. As basic knowledge is obtained it can be directly applied to biological and medical problems. This is already occurring in the connective tissue field. The number of programs in orthopedics, dermatology, rheumatology, genetic disorders, ageing and dental medicine that are studying collagen and elastin at the molecular level and the enzymes involved in the biosynthesis and degradation of collagen is rapidly increasing. The program of the Protein Chemistry Section has not only contributed information valuable to these efforts but has been an important source of training for investigators entering these health oriented areas.

Future Plans

No fundamental changes in direction are planned. Major emphasis will be placed on amino acid sequencing, particularly with regard to the location of cross-links in collagen. A comparative study of cross-links will be particularly important in understanding tissue and developmental differences. Another active area that will be explored is fibril formation and structure. This is still a topic where very little is known.

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Report of the Laboratory of Biological Structure
National Institute of Dental Research
Summary Statement

The Laboratory of Biological Structure began its existence in 1948 when the National Institute of Dental Research was first established. Research during the first 15 years, carried out by a permanent staff of 2, was centered on studies of developing and mature mineralized tissues with emphasis on training and collaborative projects. During the next 10 years as the number of investigators increased the program became more diverse. As a result it was requested and approved last year that the laboratory be divided into 4 sections making this its first full year of operation under the new organizational structure.

This recognition of separate program areas and the assignment of responsibility for each area to an investigator have strengthened the programs in thier dealings with the intramural and extramural community and have facilitated assessment of each program area, its progress, its needs, and its shortcomings. Although only a year old some of the benefits of the reorganization are apparent in the contributions each section already has made to their respective program areas (see Section Reports).

The continuing shortage in manpower and space, however, which afflict all 4 groups has precluded maximal utilization of the available talent and has hampered the development and in-depth pursuit of promising and timely new areas of research such as those presently under study in the Structural Interactions Section. To overcome some of these limitations, 3 proposals for contracts have been initiated and others are under consideration. One is concerned with the development and evaluation of fluorescent antibody reagents for filamentous oral organisms, the other 2 involve transport and physical properties of large crystals of calcium apatites and electron paramagnetic measurements of apatite crystals and mineral-protein complexes.

Direct collaborative projects also exist with the Caries Prevention and Research Branch, Veterans Administration Hospital, Connecticut; Department of Physics, Rensselaer Polytechnic Institute; the Immunology Branch, NCI; the Laboratory of Experimental Pathology, NIAMD; and the Laboratory of Physical Biology, NIAMD, as well as with the Yerkes Primate Center, Atlanta, Georgia, the Dental Research Center, University of North Carolina, and the Department of Biochemistry, School of Medicine, Vanderbilt University.

Progress has been hampered further by repeated and persistent equipment failures particularly of our 3 high resolution microscopes. A replacement for one of these, which will be installed in the near future, should hopefully eliminate many of these difficulties. It is also expected that the interfacing of the x-ray diffractometer with the NIDR computer will be completed shortly.

The present staff consists of 16 investigators, 3 of whom are guest workers paid by outside sources, and 9 persons in supporting positions as well as 2 secretaries. An indication of their dedicated efforts is provided by the fact that 24 papers, authored or co-authored by the staff, have been submitted for publication in scientific journals or books during the year. Staff members have also participated in several national and international meetings, and the Laboratory presented its entire program to the Board of Scientific Counselors during their first meeting this year.

Report of the Experimental Morphology Section*
National Institute of Dental Research
Summary Statement

The basic objectives of the Experimental Morphology Section continue to be those of advancing knowledge concerning the structure and function of cells, intercellular relationships, and extracellular products. Light and electron microscopy, electron diffraction, low temperature microincineration, enzyme cytochemistry, extra- and intracellular tracers as well as specific chemical detection methods are the principal techniques which are used.

Cell studies presently under way include: (1) examination of rat and the rat parotid gland after exposure to various experimental procedures which cause changes in the functional state of these secretory cells; (2) studies of salivary glands in the golden hamster during fetal development, maturation and senescence; and (3) demonstration of the intracellular pathway of calcium in the odontoblasts of rat molars. Progress in two of these areas will be described in more detail in this summary report.

The study of the rat parotid gland has focused on the role of lysosomes in the physiology of the gland. In addition to their role in autophagy and heterophagy, which are common to lysosomes in practically all cells, lysosomes of secretory cells appear to have at least two other specialized functions, one of which is the segregation and digestion of excess secretory material which accumulates in the cell under conditions of reduced secretory stimulation. This was first demonstrated by others in the mammotrophic-hormone-producing cell of the anterior pituitary, and subsequently in a number of other endocrine tissues. These observations have now been extended to exocrine secretory cells of the rat parotid.

By starving rats for 48-72 hours, secretory granule discharge by the parotid acinar cells was effectively inhibited. Altered secretory granules, consisting of clumps of dense material in a lighter matrix, began to appear after 16-24 hours, and were common after 48-72 hours. At the later times, altered granules had fused to form large aggregates. Both the altered granules and aggregates were cytochemically positive for acid phosphatase and non-specific esterase activity, indicating that they are part of the lysosomal system. The fate of these aggregates and the recovery of the acinar cells are presently being investigated by sacrificing animals at various times after refeeding. Preliminary results indicate that some of the acinar cells degenerate and are disposed of by tissue macrophages, while the majority recover, apparently discharging the accumulated aggregates along with the secretory granules.

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*This report is based upon progress achieved during the year in Project Nos. NIDR-LBS-72-002-(b)-(68), NIDR-LBS-72-003-(b)-(68) and NIDR-LBS-72-004-(b)-(70).

Another specialized function of lysosomes in secretory cells is the degradation of cellular membranes. Some recent evidence suggests that lysosomes may play a role in the retrieval and destruction of that excessive membranous material which is added to the plasma membrane from the secretory granules during secretion. Studies of starved-refed rats revealed the presence of numerous vesicles around the lumen of the acinus during the time it was returning to its resting size. In addition, small tubular structures and multivesicular bodies were commonly seen. At later times, many multivesicular bodies appeared to form dense bodies, and small elongated and irregular-shaped lysosomes were numerous. Although these changes in the acinar cells are difficult to follow and interpret, they may represent retrieval and degradation of redundant plasma membrane.

Future studies will determine if similar changes occur after stimulation of acinar cells with isoproterenol, and will attempt to differentiate various vesicles in the cytoplasm by their cytochemical characteristics. In addition, it is planned to extend the studies of the parotid gland to an in vitro tissue slice system.

The concept that cells associated with mineralized tissues actively transport calcium to the matrices suggests the existence of a specific intracellular pathway. Localization of this cellular calcium, however, is made difficult by its lability, which precludes the use of conventional methods for tissue processing. In an attempt to solve this problem, use was made of the facts that potassium pyroantimonate forms electron dense precipitates with cations such as Na^{+}, Ca^{++} and Mg^{++}, and that it can be added to fixatives commonly used for electron microscopy. Thus, molars of 3 to 5 day-old rats were fixed in a solution containing equal parts of either 2 or 5% osmium and 4% potassium pyroantimonate, buffered to a pH of 7.2 with 0.2 M S-collidine. The tissues were examined with the electron microscope and the electron microprobe to determine the location of the precipitates and to identify their cation content.

In odontoblasts, electron dense precipitates were localized in flattened sacs and vesicles of the Golgi region, in many of the so-called dense bodies near the secretory end, and in the distal cell processes. On the other hand, the cytoplasm, mitochondria and endoplasmic reticulum were virtually free of deposits. Evidence that the dense deposits were being brought into the cell or exteriorized was seen in a few instances. The deposits were soluble in EDTA, suggesting that they were calcium antimonate. The microprobe studies confirmed that whenever antimony was present, calcium was detected; the converse was also true. In addition, the tissues yielded higher counts for calcium when examined after osmium-antimonate fixation than following osmium fixation only. The potential usefulness of this approach is indicated by: (1) the improved retention of calcium; (2) the localization of precipitates to specific cytoplasmic structures; and (3) the quality of tissue preservation. Future studies call for an extension of these studies to other mineralizing tissues and for further experimentation with fixatives of various compositions.

Studies of intercellular relationships have been concerned with the structural and functional properties of intercellular junctions, a question which has

attracted wide attention in the last few years. Of particular interest has been the correlation of membrane modifications and associated intra- and extracellular structures with the properties of intercellular adhesion, intercellular ionic coupling, and the control of fluid and particulate movement through the intercellular spaces. In spite of this wide interest, many aspects reamin poorly understood. The present investigation was begun 2 years ago to learn more about the structure of different intercellular junctions. Using Hydra as a model, our initial studies demonstrated the complex structural organization of the septate junctions which join the outer and luminal margins of the cells in the epidermis and gastrodermis. During the past year, detailed examination of the gap junctional regions located basal to these septate junctions revealed that they consisted of several small rounded plaques of junctional particles, and that each plaque was isolated from the extracellular space by a thin band encircling the plaque. From these morphological studies it is concluded that both septate and gap junctions are important in intercellular adhesion, that septate junctions possess some barrier properties, since they exclude horseradish peroxidase and cytochrome c, and that the gap junction is better suited for intercellular ionic coupling than the septate junction.

It is planned to extend these observations of intercellular junctions to the mammalian desmosome and synapse. Preliminary evidence suggests that the intercellular material of these junctions may have an organization similar to the lattice-like structure of the septate junctions of Hydra. Thus, intercellular adhesion may be accomplished in a similar way and by similar substances in a wide spectrum of animals and locations. In addition, it would appear that the morphological specializations of the membranes and cleft of the synapse may be involved in adhesive phenomena, and that a rethinking of the current theories involving vesicle clustering, transmitter release and synaptic polarity may be in order.

The studies of extracellular products remain focused on developing and mature mineralized tissues. Our objectives in this area are shared with the Molecular Structure Section and require the capabilities of both sections. Since the specific objectives and progress of these joint ventures are detailed in the Summary Report of the Molecular Structure Section, they will not be repeated in this report. However, progress in one area, i.e., the study of inorganic constituents in collagen fibrils prior to their mineralization will be described in detail here.

A number of investigators have reported that small amounts of phosphorous can be identified in association with peptides obtained from previously mineralized human dentin, chick bone and ox bone collagen. The composition of the peptides, and their phosphorous content appear to vary considerably. Collagen preparations from the predentin zone of young rat molars and rat tail tendon were examined using excited oxygen for low temperature microincineration to (a) determine if an ash residue could be observed in association with the fibril at the electron microscopic level and (b) if inorganic constituents could be identified with the electron probe. The results indicated: following partial incineration, collagen fibrils were readily visible at the electron micro-

scopic level without staining; intermediate incineration periods revealed that portions of the fibril were more susceptible to excited oxygen thus leaving behind segments with an inherent electron density; prolonged incineration destroyed the major portion of the fibril revealing single ash deposits spaced about 680 Å apart. Electron probe studies indicated that both phosphorous and calcium could be detected in the ash from predentin and tail tendon collagen; phosphorous, however, appeared to predominate. The data confirm that collagen from mineralizing and non-mineralizing tissues contains inorganic constituents, part of which appear to be associated, in a unique way, with the fibril. In continuing this study, an attempt will be made to determine the exact location of the ash with respect to the native bonding in the fibril and to see if the "susceptible" region of the fibril represents a unique, chemically homogenous portion.

Report of the Experimental Pharmacology Section*
National Institute of Dental Research
Summary Statement

The interest and research efforts of the Experimental Pharmacology Section revolve about the field of mammalian organogenesis, and are particularly well exemplified by our continuing studies of the etiology and pathogenesis of cleft palate and related abnormalities of development. In the past we have been able to produce congenital malformations of the oral-facial region with benzhydrylpiperazines, vitamin A and lathyrogens. Although these agents produce a fairly specific "syndrome" of malformations in a given species, they are not necessarily teratogenic in all species.

The "goal" in experimental teratology is to produce malformed young; however, the aim of the Experimental Pharmacology Section is by no means this restricted. If the production of the congenital malformation is to have any scientific value, a multidisciplinary approach has to be used to understand the mechanism of action at the teratogenic stimulus, to define interspecies differences or parallelisms in the response to the stimulus, and eventually to relate the experimental situation to the occurrence of the malformation in man. In addition it would be desirable to obtain an animal model with cleft palate that would lend itself to experimental surgical procedures in order to establish better rehabilitation for the human with this malformation.

Work has, and is being carried out attempting to induce specific defects and, if possible, the malformation of cleft palate alone, in order to evaluate its etiology. The approach to the problem, involves studies in the pharmacodynamics, metabolism, placental transfer and fetal response to a particular drug.

Specifically we have blocked or enhanced effects of the teratogens by enzyme system stimulation or by altering metabolic pathways. We have studied the interspecies response to the different drugs and the comparative pathology of the lesions produced.

Benzhydrylpiperazine teratogens: The teratogenic effects of norchlorcyclizine, its analogs and Ca^{2+}-chelating agents were determined after intrauterine administration to the rat embryo. Application of norchlorcyclizine (60 µg) on day 15 of gestation produced cleft palate and limb malformations in 5.9% of the viable fetuses; co-application with 20 µg of either Na_4EDTA or a more specific Ca-chelator, Na_2H_2 EDTA resulted in 32.0% and 16.2% malformed fetuses, respectively. However, when Ca_2 EDTA (20 µg) and norchlorcyclizine were

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*This report is based upon progress achieved during the year in Project Nos. NIDR-LBS-72-016-(b)-(63), NIDR-LBS-72-017-(b)-(63), and NIDR-LBS-72-018-(b)-(63).

co-applied only 2.1% of the fetuses were malformed. The chelating agents administered alone produced no malformations. The in vivo embryonic uptake of ^{14}C-chlorcyclizine applied alone on day 15 of gestation was 700 ± 200 cpm/g of embryo, while co-administration of Na_4 EDTA increased the uptake to 1800 ± 250 cpm/g. Conversely, the uptake of $^{45}CaCl$ was 2000 ± 200 cpm/g in the control 15 day embryo but only 800 ± 175 cpm/g in the malformed embryo. Previous in vitro work indicated that Ca^{++} and positively charged benzhydrylpiperazine teratogens could bind competitively to the same sites in bovine nasal septum cartilage (Progress Report 1970). These findings suggest that chelation of Ca^{++} in the embryo allows benzhydrylpiperazine teratogens to bind to sites normally occupied by Ca^{++}, and this may account for the developmental anomalies observed.

Lathyrogens: Lathyrogens have been demonstrated to be potent teratogens in the rat. Last year the fact was reported that β-aminopropionitrile (BAPN) was teratogenic in the rat but not in the rabbit, presumably because the adult rabbit metabolizes BAPN very rapidly to non-teratogenic cyanoacetic acid. Work during the past year demonstrated that significant differences in the rate of metabolism also occurred in different strains of mice, different species of subhuman primates and in calves. Furthermore, no clear cut relationship was found between the size of the animal and the rate of BAPN metabolism. However, the rate of BAPN conversion to cyanoacetic acid, could be controlled by pre-administration of isoniazid HCl (INH). In all species tested the rate of BAPN metabolism was markedly reduced. In the rat, after pretreatment with INH only 1/5 of the original BAPN does was required to elicit a 100% cleft palate response. INH was not teratogenic at the doses used and did not inhibit the crosslinking of embryonic collagen -- this inhibition of crosslinking was in every case related to the amount of BAPN in the embryo. Although INH is structurally related to iponiazid, a strong monamine oxidase (MAO) inhibitor, it has not previously been shown to be a very effective MAO inhibitor. In vitro (and in some cases in vivo) enzymatic experiments indicated that the BAPN-converting enzyme(s) is present in the uterus> lung> placenta> liver> kidney but could not be detected in the 15 day embryo or in the maternal serum. In the liver the enzyme(s) present in the 105,000 g supernatant accounted for about 75% of the activity with about 25% of the activity found in the 9,000 g pellet. However, in the uterus (a tissue rich in collagen) the 9,000 g pellet exhibited more activity than did the supernatant. INH competitively inhibited the enzyme(s) as did iponiazid, INH however, was about 3 times as effective as iponiazid.

BAPN is also a specific inhibitor of collagen crosslinking, so a study was undertaken in order to determine whether or not BAPN alters collagen crosslinking or synthesis in the palatal shelf itself. Palatal shelves were labeled in vitro with ^{14}C-proline and collagen synthesis was determined by measuring the amount of ^{14}C-hydroxyproline (HYP) in the palate, while collagen crosslinking was determined by the amount of ^{14}C-HYP found in the neutral-salt soluble fraction from the palate. Acid mucopolysaccharide (AMPS) synthesis was followed using ^{3}H-glucosamine incorporation with isolation of the labeled AMPS by DEAE-cellulose chromatography. BAPN was administered orally at 600 mg/kg on day 15, and at various intervals palates were dissected

out and labeled in vitro for 1-2 hours to determine the effect of in vivo treatment. It was found that collagen crosslinking was inhibited in the palate 6 hours after BAPN was administered, but not after 30 hours. When BAPN was added in vitro, the crosslinking of palatal collagen was inhibited, although synthesis was not affected. Two-thirds of the AMPS synthesized in the palate consisted of hyaluronic acid while the remaining fraction was sulfated mucopolysaccharides. The synthesis of AMPS in the palate was not altered by BAPN. The results indicate that BAPN inhibits collagen crosslinking, but not synthesis, in the secondary palate at the time when BAPN induces cleft palate.

Three collaborative projects are being planned for the coming fiscal year.
1. Yerkes Primate Center, Atlanta, Ga. Dr. McClure: Preliminary studies have demonstrated that the rhesus monkey metabolizes BAPN much faster than the rat. However, if the lathyrogen administration is divided into two daily doses co-administered with isoniazid, then a blood level comparable to the one that is teratogenic in the rat is obtained. Timed pregnancies are planned in this primate in order to determine whether it also is susceptible to the teratogenic action of the compound. Once this is established other biochemical studies on placental transfer and fetal disposition of the drug will be planned.

2. Dental Research Center, N. C. Drs. G. Smiley and G. Mechanic: A collaborative study is planned to determine the chemical nature of the collagen crosslinks in the palate as a function of both gestational age and the effects of BAPN.

3. Vanderbilt U., Nashville, Tenn., Dept. of Biochemistry, School of Medicine. Dr. S. Cohen: An epidermal growth factor has been isolated by Dr. Cohen from the mouse submaxillary gland which when injected into new born rats causes accelerated eyelid opening. This factor, a protein (M. W. 20,000), has been shown to act by stimulating epidermal cell proliferation and keratinization. In vitro and in vivo studies are planned to determine the effect of this factor on palatal epithelial break down that normally occurs during palatal fusion.

In addition to these collaborative projects the staff of the section intends to work on the etiology of cleft palate formation by screening suspected teratogens in different species. The mechanism of action of established teratogens will be investigated (i.e., attempts will be made to isolate the BAPN metabolizing enzyme from the placenta and uterus, and to determine the nature of the inhibitory action of isoniazid on BAPN and its relation to collagen maturation).

Studies are also in progress to examine the important biochemical and morphological events involved in palate fusion, especially the role of macromolecules such as collagen and acid mucopolysaccharides. Further attempts will be carried out to identify the common embryonic binding site(s) for norchlorcyclizine and calcium, and to determine how these can interfere with normal palatal rotation.

Report of the Molecular Structure Section*
National Institute of Dental Research
Summary Statement

The principal objective of the Molecular Structure Section is to conduct basic investigations of the ultrastructural and physico-chemical properties of calcified tissues and related soft tissue structures. A corollary but equally important goal is the study of naturally occurring and synthetic calcium phosphate compounds related to the mineral components of hard tissue. Recent efforts have been focused on both the collagenous as well as the mineral components of calcified tissue, but during the past year it was the mineral components and their synthetic analogues that received particular attention.

X-ray line broadening analysis is the principal non-destructive means by which the size of apatite crystals in mineralized tissue can be measured. Several different methods are available for extracting this parameter from x-ray diffraction data. However, the results from previous applications of these methods have not been consistently comparable. A study to evaluate the different line broadening techniques and resolve past discrepancies in results was completed this past year. The three most common line breadth methods, (1) Fourier, (2) Variance, and (3) Integral Breadth, were evaluated using calcified turkey leg tendon as a model. The results showed that, when properly employed, the three methods can give compatible results. Methods (1) and (2) gave estimates of the mean length along the c-axis of the apatite crystals averaging 215 A. Method (3) gave a value of 409 A for this length. The apparent disparity between the result of method (3) when compared with the results of methods (1) and (2) is not due to experimental error but, instead, reflects the existence of a wide distribution in the size of apatite crystals in hard tissue. The results also indicate that some internal strain is present in these crystals. The size estimates obtained in this study were smaller than those seen in an earlier electron microscopic examination of turkey leg tendon. This discrepancy suggests that the apparently single particles seen in electron micrographs may consist of many smaller crystalline domains.

X-ray line broadening analysis is one of few measurements of vertebrate mineral that can be reliably made in the presence of protein. But for many physical and chemical measurements, better results can be obtained if the

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*This report is based upon progress achieved during the year in Project Nos. NIDR-LBS-72-008-(b)-(69), NIDR-LBS-72-009-(b)-(71), NIDR-LBS-72-010-(b)-(70), NIDR-LBS-72-011-(b)-(71), NIDR-LBS-72-012-(b)-(68), NIDR-LBS-72-013-(b)-(68), NIDR-LBS-72-014-(b)-(70) and NIDR-LBS-72-015-(b)-(63).

protein is removed beforehand. Existing deproteination procedures, however, have proven to be less than optimally effective. The solvents used in these procedures cannot be made sufficiently anhydrous to prevent major physical and chemical alterations from occurring in the mineral during extraction. A study to test the efficacy of purified hydrazine reagent as a hard tissue deproteinator was initiated this past year. This solvent was judged to be potentially more effective because it could be utilized under more anhydrous conditions. The results to date are promising. Hydrazine has proven to be a very effective deproteinator. Resultant anorganic bones were found to contain less than 0.3% nondialyzable protein, i.e., an approximately 100-fold reduction in protein content. The apatite crystals in these bones did not change in mean size, nor did any of the amorphous moiety convert into apatite. No changes in Ca/PO_4 molar ratio were detected and there were only slight reductions in HPO_4^{-2} and CO_3^{-2} levels, much less than occur in bone mineral washed with water.

The isolation of amorphous calcium phosphate (ACP) from crystalline apatite in hard tissue has yet to be achieved, although the success of the hydrazine treatment is a necessary first step toward this goal. Consequently, studies on synthetic analogues are still the major means by which reliable predictions as to the nature of *in vivo* amorphous calcium phosphate are possible. Current studies on synthetic ACP have vividly revealed the structural and chemical complexities of this substance and the close association it establishes with crystalline apatite upon conversion into the latter.

Electron microscopic studies conducted during this past year showed that dried ACP can occur in disk-like shapes, as well as in the more familiar ball-like configurations. These two morphological forms were found to be intimately related and were, in part, artifacts of drying. These results suggest that ACP is loosely structured and highly hydrated in solution. When allowed to remain in solution, ACP converts into apatite. Electron microscopy revealed a close association between these two moieties during conversion. The first apatite crystals appeared on the surface of the amorphous particles, and the entire crystallization process was highly localized about the space surrounding the amorphous aggregates. Yet there was little invasion of the apatite into the space previously occupied by the amorphous phase, indicating that *in situ* solid-state transformation of ACP into apatite is not likely, but that the ACP does initiate and control the conversion process.

Chemical studies conducted during the past year showed that the constancy in reported values for the Ca/PO_4 molar ratio of ACP at or near 1.50 was in part an artifact of sample washing. The ratio of unwashed ACP samples varied from 1.18 to 1.50 depending upon the pH of the preparation, the higher ratios being associated with larger pH values. This departure of the ratio from 1.5 was due in part to the presence of a labile chemical fraction rich in HPO_4^{-2} and low in calcium, which was irreversibly lost during washing. Crystalline apatite was found not to have such an irreplaceable fraction but was, however, observed to contain large amounts of readily replaceable, surface oriented HPO_4^{-2}. Previous proposals to account for the finding that the Ca/PO_4 molar

ratio in biological apatites was generally lower in value than expected, involve complicated internal crystal defect and/or intracrystal layering models. The above studies indicate, however, that this low ratio could simply be due to the presence of surface HPO_4^{-2} ions.

Even after the labile component was removed by washing, synthetic ACP was found to contain amounts of HPO_4^{-2} varying inversely with the pH of the preparative medium. In addition, carbonate was found in all amorphous preparations. Its concentration in these solids increased with increasing preparative pH and with increasing solution CO_3/PO_4 ratio. Since HPO_4^{-2} and CO_3^{-2} have opposing effects on the overall Ca/PO_4 molar ratio of ACP (HPO_4^{-2} lowering and CO_3^{-2} raising it), a whole family of ACP materials having inversely varying amounts of HPO_4^{-2} and CO_3^{-2} can possess identical Ca/P ratios.

An important part of this section's ongoing activities has been that of participating in collaborative studies. Two such efforts during the past year were particularly noteworthy.

In conjunction with Dr. G. G. Glenner, NIAMD, infrared spectroscopy was employed to confirm the presence of antiparallel-folded polypeptide chains in a β-pleated sheet conformation in human amyloid protein fibrils. In this same study, both infrared spectroscopy and x-ray diffraction were used to determine the β-pleated sheet content of immunoglobulins in the solid state. It was found that the variable portions of heavy and light chains of immunoglobulin were the most easily capable of assuming the β-conformation. In fact, the variable region of the light chains was most like amyloid in its infrared and x-ray properties. This finding is compatible with the chemical homology existing between these two peptides.

In collaboration with Dr. M. H. Gottlieb, NIAMD, the influence of electrolytes on lamellar lecithin mesophases is being studied by x-ray diffraction procedures. To date, it has been found that electrolytes have small and variable effects on the thickness of the phospholipid bilayers, suggesting it is unlikely that electrolytes alone would strongly affect the permeability of phospholipid-protein membranes.

Historically, x-ray diffraction and infrared spectroscopy have been the principal investigative tools used in our section, but in recent years a more comprehensive methodology has developed, utilizing synthetic and analytic chemical procedures as well as electron microscopy and other instrumental approaches. The most notable event this past year with regard to our expanding methodology was the acquisition of two major pieces of spectrometric equipment, respectively for far-infrared and Raman studies. Several new procedural innovations were also developed during the past year to enable the most effective utilization of these new spectrometers in our research program.

With the exception of the x-ray line broadening study of turkey leg tendon, which is now complete, the projects comprising this sectional report will continue during the coming year. Even the line broadening study leaves a

legacy, in that future studies are planned for investigating the discrepancy noted above between the diffraction and the microscopy estimates of the size of biological apatite crystals. The hydrazine procedure for removing protein will enable our section to more effectively characterize bone mineral. Electron microscopic elucidation of ACP in deproteinated bone mineral is planned. With prior hydrazine extraction, spectroscopic procedures can now be applied to vertebrate mineral without protein interference, and studies utilizing this procedure will also be carried out. Our new spectroscopy equipment will also make possible more definitive examination of the inorganic phases in bones and teeth, and of synthetic apatitic and amorphous calcium phosphates.

Report of the Structural Interactions Section*
National Institute of Dental Research
Summary Statement

In a striking but timely departure from its prior focus of interest on macromolecular structure, the Section on Structural Interactions in the Laboratory of Biological Structure has become increasingly aware of the significance of the oral bacterial flora as the probable cause of caries and periodontal disease. We have therefore turned our attention to two new lines of research, each an entity within itself but still intimately related to one another. The first is concerned with the rapid identification of specific oral microorganisms, while the second is an effort to define innovative biological methods of dental plaque control. The following report details much of the progress made in the past year.

Epidemiological surveys suggest that bacterial deposits play an etiologic role in both periodontal disease and root surface caries. Since 35% of the cultivable organisms from gingival deposits are gram positive filament forming bacteria, comprising the genera Actinomyces, Rothia, Lactobacillus, Arachnia, Propionibacterium, Bifidobacterium, Corynebacterium and Bacterionema, and since certain of these, Actinomyces naeslundii and Actinomyces viscosus, have been shown to induce periodontal lesions and root surface caries in gnotobiotic rats, the latter two species have received most attention from this section. In order to determine the potential pathogenicity of a specific organism, it is necessary to establish their relative proportion in normal individuals as well as in those with severe periodontitis. Historically, this has been accomplished by conventional morphological, biochemical and serological methodology, which is not only time consuming, but does not lend itself to sampling large populations. Immunofluorescence, on the other hand, permits direct visualization of specific organisms and has advantages of simplicity, rapidity and exquisite sensitivity. In the past, however, it has been strictly a qualitative technique.

The project under investigation involves development of fluorescent antibody (FA) reagents specific to the oral actinomycete-like bacteria, and development of a quantitative immunofluorescent method so that epidemiological studies concerning the etiologic role of these bacteria in human oral disease can be carried out.

High titer antiserum to a human strain of A. viscosus was produced in rabbits and conjugated with fluorescein isothiocyanate. Cross reactions to A. israeli serotype 1 and A. naeslundii were eliminated by absorption. Microcolonies of A. viscosus growing on agar plates were stained with the high titer specific antiserum, and subsequently examined by incident ultraviolet light. Microscopically detectable 18-24 hr old colonies, as well as older mature colonies,

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*This report is based upon progress achieved during the year in Project Reports No. NIDR-LBS-72-006-(b)-(68) and NIDR-LBS-72-007-(b)-(69)

displayed yellow-green fluorescence. In mixed cultures A. viscosus could be readily detected even when overgrown by other microorganisms. Preliminary studies involving human plaque samples indicate that this method selectively and rapidly identifies colonies of A. viscosus.

The conjugate was also used for direct microscopic counts of samples using both dark field and fluorescent illumination. Individual cells of A. viscosus could readily be identified in smears of mixed samples. The slide technique may well be the method of choice, since it requires less conjugate and allows the smear to be made directly as it is obtained from the oral cavity, while the addition of conjugate and subsequent observation can be made at a later time.

The ability of a specific microorganism to cause oral disease is at least partly dependent upon its production of one or more substances which allow the organism to maintain itself in a specific site for relatively long periods of time. The oral streptococci and filament-like bacteria are notable examples of this since they both form a tenaciously adherent plaque on the surface of the tooth, the former predominantly on the free enamel surfaces, the latter near or even beneath the gingival margin. It would seem, therefore, that control and eradication of caries and periodontal disease hinge on the removal or inhibition of plaque formation. If a chemical substance can be found which prevents the formation of adherent deposits or removes established deposits, a big step toward control of caries and periodontal disease would be achieved. A possibility, which has not been explored previously, is that such a substance may be produced by specific microorganisms. The Section on Structural Interactions, therefore, has proceeded on the assumption that certain microorganisms produce inhibitors to microbial plaque formation and that these organisms can be identified and the inhibitory substance isolated.

To date, we have isolated at least one organism, a Gram positive coccus designated S4, which produces such an inhibitor. Comparisons between the ability of numerous streptococci and diphtheroids to form in vitro plaque in the presence or absence of the inhibitory substance revealed considerable plaque deposits in the control tubes, but none when the organisms were grown either in media containing S4, in media in which S4 had previously been grown but which was sterilized by boiling or autoclaving, or in filtered supernatent from S4 cultures.

A direct relationship between growth of S4 and its elaboration of the inhibitory material in medium was demonstrated. After 5 hours incubation S4 had elaborated sufficient inhibitory material into the medium to substantially inhibit in vitro plaque formation by 5 strains of filamentous diphtheroids. After 10 hours incubation of S4 in basal medium, the supernate totally inhibited in vitro plaque formation.

This inhibitory property of the S4 supernatant was found to be dialyzable indicating it probably had a molecular weight of less than 10,000.

The isolation of an organism capable of producing a substance which inhibits *in vitro* plaque formation has led us to increase our efforts toward developing a rapid method for screening large numbers of organisms for their anti-plaque properties. Such a method has been worked out and it appears to be relatively reliable; that is, organisms which are selected by this screening technique and tested further, frequently exhibit anti-plaque activity *in vitro*.

The efforts of the section for the coming year will concentrate on: (1) Further expansion and testing of the FA technique to develop it as a rapid method for determination of specific organisms in large human populations. Excellent progress has been made and several contracts are being considered for the development and evaluation of fluorescent antibody conjugates for *Arachnia propionica*, *Rothia dentocariosa*, *Actinomyces odontolyticus* and *A. naeslundii*; and (2) Standardization of screening procedures for biologically produced agents inhibitory to plaque formation by specific streptococci and filamentous diphtheroids associated with caries and periodontal disease. Isolation and characterization of such inhibitory substances produced by certain organisms will also be carried out.

Report of the Laboratory of Microbiology and Immunology
National Institute of Dental Research
Summary Statement*

It is timely to recall that this Laboratory has evolved over the past dozen years or so from a group of investigators with extremely diverse interests in microbiology in to three highly productive sections which are contributing consistently and meaningfully to their respective scientific disciplines. The Immunology Section is involved in research on defining more precisely the role of humoral and cellular immunological factors in the acute and chronic inflammatory response, while the programs in the Virology Section are applying similar techniques and approaches to the exploration of virus-induced immunopathology. Our Microbial Physiology Section is providing a clearer understanding of ecological and evolutionary relationships among oral microorganisms as well as metabolic control mechanisms operating within the bacterial cell.

Oral soft tissue diseases, which include chronic periodontitis and virus-induced lesions, continue to be problems of major concern in this and other dental research facilities. It is important to point out that while the research in this Laboratory has been contributing to, and has had a considerable impact on, the mainstream of science in Microbiology and Immunology in general, it has nevertheless also contributed significantly to the mission of the National Institute of Dental Research by applying this knowledge to problems of oral soft tissue pathology. Over the past year our program leaders have participated in International Symposia and meetings concerned with oral biology, host resistance mechanisms, delayed hypersensitivity, immune complex diseases and virus-induced immunopathology. Several extensive reviews on these subjects have been contributed to the literature by our staff as a result of such meetings. Ample documentation of these contributions is provided in the summary Section reports which follow.

Because of space and manpower limitations in this Laboratory, two proposals for contracts have been initiated with a view of extending our observations on the role of infectious virus-antibody complexes and delayed hypersensitivity in human oral immunopathology. The latter proposal is particularly important in order to expand our newer knowledge on pathogenetic mechanisms in periodontal disease which suggests that biologically-active effector molecules from lymphocytes can account for a number of events in chronic periodontitis, including bone resorption.

Since it is obvious that a major commitment to immunology is an important component of the intramural research program of this Institute, plans have been set in motion which would result in the restructuring of immunology into two Sections: Cellular Immunology and Immunopathology. In view of the broad scope of present and projected immunologic research in this Institute,

*This report is based upon progress achieved during the year in Project No. NIDR-LMI-72-001-(b)-(65)

involving collaboration of investigators in various Laboratories, other Institutes, and outside institutions, the establishment of these two Sections is important to facilitate required flexibility of programming and to effect considerable saving in administrative detail.

Report of the Microbial Physiology Section
National Institute of Dental Research
Summary Statement*

The Microbial Physiology Section has continued its studies on fundamental mechanisms by which the biochemical activities of the microbial cell are regulated. These studies have been conducted with both cariogenic and non-cariogenic microorganisms with a view toward, 1) establishing general principles of cellular control processes, and 2) possibly uncovering unique aspects of cellular metabolism in cariogenic organisms that would help define their pathogenicity in precise biochemical terms. These studies have the long range goal of establishing a rational basis for the design of antimetabolities or other chemotherapeutic agents that would be specific for altering cellular activities associated with pathogenesis.

Streptococcus faecalis

For the past several years an effort has been underway to resolve the means by which S. faecalis is able to metabolize glucose more or less exclusively via the Embden-Meyerhof pathway, with the stoichiometric accumulation of lactate, under conditions where this organism has high constitutive levels of the enzymes of the hexosemonophosphate pathway. Certain specific aspects of this problem were summarized in last year's report. This year we have expanded these studies and have arrived at a rather comprehensive understanding of the overall process, the details of which have been published (1,2). Results from in vitro studies with individual enzymes have led to the advancement of the following hypothesis: Preferential channelling of glucose carbon through the Embden-Meyerhof pathway appears to be accomplished in S. faecalis by the specific interaction of fructose-1,6-diphosphate (FDP) with a key enzyme from each of the two pathways, which results in differential alterations of their catalytic activity. The Embden-Meyerhof pathway enzyme, lactate dehydrogenase (LDH), is completely dependent upon FDP for catalytic activity, whereas the hexose-monophosphate pathway enzyme, 6-phosphogluconate dehydrogenase is strongly inhibited by FDP. Thus, under conditions where a sufficient intracellular pool of FDP is present to activate the LDH, the activity of 6-phosphogluconate dehydrogenase (6PGD) is presumably restricted. A prediction of this hypothesis is that any condition that would lower the FDP pool would result in a shift of the glucose fermentation away from lactate production. This prediction has been tested and confirmed by P. J. VanDemark at Cornell University. VanDemark and colleagues (3) have grown S. faecalis in the chemostat and found several conditions which led to a reduced production of lactate from glucose. Under each of these conditions, the intracellular concentration of FDP was greatly reduced from that found under growth conditions that favored a stoichiometric accumulation of lactate from glucose.

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*This report is based upon progress achieved during the year in Project Nos. NIDR-LMI-72-010-(b)-(66), NIDR-LMI-72-011-(b)-(61), NIDR-LMI-72-012-(b)-(72), NIDR-LMI-72-013-(b)-(61), and NIDR-LMI-72-014-(b)-(66).

The mechanism by which FDP inhibits the activity of 6PGD has been studied in considerable detail. Last year a procedure for purifying this enzyme to a state of homogeneity was reported, as well as some of its physical properties. This year a comprehensive kinetic analysis of the purified enzyme was undertaken. The negative effector, FDP, has been shown to be an S-hyperbolic competitive inhibitor with respect to the substrate, 6-phosphogluconate, and an I-hyperbolic, S-hyperbolic noncompetitive inhibitor with respect to the coenzyme, NADP. These and other data support previous studies which suggested that FDP interacts with the 6PGD at a site distinct from the catalytic site.

Other studies with the 6PGD have suggested that FDP may exert its effect by mediating either an isomerization or a depolymerization of the enzyme. The former mechanism is currently favored on the basis of the fact that the enzyme does not undergo a molecular weight change in the presence of FDP. The negative effector does, however, protect the enzyme from inactivation by certain sulfhydryl reagents.

Streptococcus mutans

The widespread use of mannitol and sorbitol fermentative ability as a phenotypic characteristic for distinguishing S. mutans from certain other oral streptococci has prompted an inquiry into the means by which S. mutans catabolizes these compounds. The available data indicate that S. mutans NCTC 10449 ferments both mannitol and sorbitol by a pathway that involves phosphorylation of the substrates prior to their oxidation by distinct, inducible hexitol phosphate dehydrogenases to the common glycolytic intermediate, fructose-6-phosphate (4).

Another line of investigation with S. mutans has dealt with the synthesis of extracellular and intracellular polysaccharide by these organisms. This study is in a very preliminary stage, but a promising observation has already been made. It is well known that S. mutans grown in a complex medium produces both cell-associated and soluble dextransucrase. When S. mutans 6715 is grown in a chemically defined medium, however, little if any dextransucrase is found in the culture supernatant, although cell-associated enzyme can be readily demonstrated. This observation raises the provocative question of whether these organisms possess a specific "release" mechanism by which they can control the relative distribution of cell-associated and soluble dextransucrose.

Taxonomic Studies

Work in the area of systematic bacteriology has continued as an important phase of the Section's overall program. This year about 150 strains of Lactobacillus, Pediococcus, and Leuconostoc comprising type, neotype and important reference strains have been checked for authenticity by generally accepted tests and techniques. In addition, and as a prerequisite for rewriting the description of thirteen separate genera for the eighth edition of Bergey's Manual, it was necessary to reexamine a number of different organisms. This task has been completed and the results published (5-10).

Evolution of lactic acid bacteria

A study initiated several years ago to assess phylogenetic relationships among the lactic acid bacteria continues to provide new insight into the evolution of this group of organisms. This study began with an extensive characterization of an inducible malic enzyme found among certain group D streptococci and strains of Lactobacillus casei (11). Using antisera prepared against the homogeneous enzyme from S. faecalis, it was established that a high level of structural homology existed between the malic enzymes from the two organisms (12). This work led to the formulation of some general principles which served as guidelines for the selection of a structurally conserved protein, fructose diphosphate aldolase, for more extensive studies.

The FDP aldolase has been purified from extracts of S. faecalis to a state of homogeneity and many of its physical and chemical properties have been characterized. Antiserum prepared against this enzyme has been used to survey a large number of species of lactic acid bacteria to determine to what degree their FDP aldolases are immunologically homologous to the enzyme from S. faecalis. It has been found that members of the genera Streptococcus, Pediococcus, Lactobacillus, Diplococcus, and Microbacterium are interrelated, and a rough phylogenetic hierarchy has been assembled.

It is important to note that the lactic acid bacteria group contains a number of pathogens which produce a wide variety of diseases, including bacterial pneumonia, endocarditis, rheumatoid arthritis and dental caries. Since a natural relationship has now been demonstrated for this group of microorganisms, the positioning of these pathogenic lactic acid bacteria in a phylogenetic map may provide some insight into the evolution of these organisms from harmless saprophytic ancestral forms. Perhaps, of more immediate interest, one may now begin to study the evolution of invasive mechanisms from precursor molecules not originally involved in infectious processes.

In general the studies summarized in this report will be continued. Specifically, studies relating to the regulation of carbohydrate metabolism in the cariogenic and noncariogenic bacteria will be expanded to include work on the enzyme pyruvate kinase. This enzyme is a major control site in the regulation of glycolysis and gluconeogenesis in mammalian systems and may be important in the regulation of microbial intracellular polysaccharide formation. The possibility that the enzyme dextransucrase is released from S. mutans cells only under certain specified conditions will be studied in more detail. Studies on the evolution of bacteria will also be expanded and a more rigorous positioning of the various species under examination will be attempted through the use of microcomplement fixation and quantitative precipitation procedures.

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Report of the Immunology Section
National Institute of Dental Research
Summary Statement*

The investigations of the Immunology Section all focus on understanding the mechanisms operating at the level of cell and cell-product interactions that serve to control the magnitude of immunological reactions, and how such immunological reactions are involved in normal and abnormal inflammatory reactions. The central concept on which the studies focus is that there are two lymphoid populations responsible for diverse types of immunological responses. The first consists of bone marrow derived sessile lymphoid and plasma cells (B cells) that make specific humoral antibodies. The latter may combine with antigens, and the resultant antibody-antigen complexes may then activate the complement sequence which results in acute inflammatory and anaphylactic reactions. The other lymphoid population is the thymic dependent (T cell) which recirculates and is activated directly by contact with antigens. This immune population either causes chronic delayed inflammatory reactions by direct contact lysis of target antigens, or by production of numerous non-specific factors which are "mediators of cellular immunity". Appropriate interactions between these two immune populations can result in either the expression or suppression of immunological reactions.

B and T cell interactions are readily studied in bursectomized chickens which have only T cell dependent immune reactions. Drs. R. Jacobs and J. J. Oppenheim in collaboration with Dr. M. Blaese (NCI, NIH) have found that the in vitro lymphoproliferative reactions of bursectomized agamma-globulinemic chickens (B cell deficient) can be specifically suppressed by antibodies. Thus, a B cell product (antibodies), by competitively binding antigens, blocks them from activating T cells, which suggests that antibodies can have a feed-back control effect on cellular immune reactions.

Dr. H. Kirchner has continued these studies and has been successful in culturing chicken spleen cells in artificial medium (RPMI 1640) without serum supplementation. He has found that chemically bursectomized (1-3 day-old cyclophosphamide-treated) chickens manifest normal in vitro lymphocyte reactions to many nonspecific stimulants indicating that they apparently have normal T cell functions. However, their reaction to sensitizing antigens inexplicably are significantly impaired. This suggests that B cells or their products may also be involved in turn in facilitating the initial activation of T cells. Reconstitution studies are in progress to resolve this fascinating riddle.

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The interaction of lymphocyte (T cell) and antibody reactions (B cell) is also being studied in human allergies. In collaboration with Dr. S. Leikin of D. C. Children's Hospital and Dr. Halla Brown of the George Washington Medical School, a positive in vitro lymphoproliferative response of allergic patients to Alternaria and animal danders has been observed. With hyposensitization therapy antibodies appear in their plasma which specifically block these in vitro lymphocyte reactions. The contribution of lymphocytes in acute allergic reactions requires further elucidation.

The macrophage has also been reported by others to facilitate production of antibody responses in vivo. Drs. R. Seeger and J.J. Oppenheim have reported that macrophages facilitate lymphoproliferative respones in vitro, and induce delayed hypersensitivity when injected with antigens into guinea pigs. The effects of three factors that regulate induction of immunity by macrophage-antigen (m-Ag) were studied. Administration of a mixture of an excess of soluble unbound antigen with m-Ag interfered with induction of delayed hypersensitivity (DH) and enhanced the antibody response. This supports our hypothesis that m-Ag preferentially activates T but not B cells, whereas, soluble antigens do the reverse, and may in addition directly interfere with T cell activation. Alternatively the resultant antibody may have suppressed DH. This latter notion was tested by immunizing guinea pigs with a mixture of antibodies and macrophage-antigen. Antibody excess blocked induction of both DH and antibody production, indicating the importance of presence of antibody in regulating the immune response of both T and B cells. Finally, when macrophages were incubated with a pulse of antigen for 1 to 3 days, rather than the optimal time of 90 min, they destroy antigen, and the residual antigen was found to be less immunogenic. This indicates that macrophages play a dual role of enhancing as well as resolving immune reactions by degrading and eliminating the antigenic stimulants.

Interactions of T and B cells also modulate transplant and tumor rejection. Drs. R. Gordon, D. Ranney and J. J. Oppenheim in conjunction with Dr. E. Stinson (NHLI, NIH) and Dr. M. Mage (NCI, NIH) have investigated the mechanism by which alloantisera made by B cells suppress T cell mediated transplant rejection and prolong heart grafts in rats. These alloantisera specifically suppress the appropriate in vitro mixed leucocyte reaction. Utilization of this assay has permitted us to determine that the inhibitor is in the IgG fraction (as determined by DEAE chromatography) of rat serum. The antibody inhibits the "stimulator" cells, indicating that the mechanism of action is competitive and reversible rather than by permanently inactivating the responder cells.

Dr. J. Pincus is continuing studies of the isolation and characterization of murine histocompatibility antigens ($H\text{-}2^d$) from L 1210 tissue culture cells. Progress has been made in that larger quantities of these cells or $H\text{-}2^d$ extracts are being supplied on contract by Associated Biomedic Systems, Inc., of Buffalo, N. Y. (#NIDR-71-2385). The yield of surface antigen has been increased to 10% of the cell content. A probit analysis was developed in conjunction with the contractor to accurately measure the antigen content of the extracts.

Progress in obtaining biological effects of soluble H_2 antigens pursued by Drs. R. Gordon, D. Ranney and J. J. Oppenheim has been limited. Stimulation of cultured allogeneic lymphocytes by H-2^d soluble antigens has been meager. Immunization with soluble antigen has produced hemagglutinating antibodies (activated B cells), foot swelling (a delayed reaction) and slightly increased the rate of graft rejection (indicative of T cell activation), but a variety of experimental approaches have failed to produce the desired prolongation of graft survival (tolerance).

Tumor immunity is also being studied by Dr. J. J. Oppenheim in collaboration with Drs. M. Metzer, R. Herberman, R. Smith and I. Yust (all of NCI, NIH). Peripheral leucocytes from one of six patients with melanoma were found to specifically inhibit in vitro DNA synthesis in several allogeneic tissue culture melanoma lines, and to release more Cr^{51} from such cells than was released by nonimmune leucocytes. Tissue culture lines of breast tumor cells were not inhibited or lysed to any greater degree by this patient's leucocytes. The immune patient also had circulating antibodies which were cytotoxic for normal allogeneic lymphocytes, and "LDA" antibodies that increased the cytotoxic effect of normal lymphocytes on melanoma target cells. Despite this abundant evidence of immune reactivity to tissue antigens, the patient died. We are pursuing investigations of relationship of various in vitro assays of tumor immunity to actual in vivo defense mechanisms.

Studies of lymphocyte mediated inflammation in periodontal disease (P.D.) are being pursued by Drs. J. Horton, J. J. Oppenheim and S. Mergenhagen. A direct correlation has been found between the degree of in vitro lymphocyte transformation by dental plaque material and the degree of periodontal inflammation of the leucocyte donor. The supernatants of leucocyte cultures from P.D. patients stimulated by plaque were found to contain "lymphotoxin" which is cytotoxic when added to tissue cultures of mouse or human fibroblasts. This may reflect the mechanism of tissue destruction seen in P.D. The leucocyte culture supernatants, when added to bone cultures were also found to activate osteoclasts to resorb fetal rat bone. This may reflect the mechanism of bone resorption in P.D.

The mechanisms by which cell mediated immunological reactions may produce accumulations of inflammatory cells are being investigated by Drs. L. Altman and S. Mergenhagen. It has been found that, in addition to a complement fragment, C5a, which is chemotactic for monocytes and granulocytes, supernatants of mitogen or antigen stimulated leucocyte cultures also contain factors chemotactic for these cells. The biochemical nature of these factors is being determined.

Dr. W. Hook is studying immunological mechanisms of histamine release in inflammation. Incubation of hamster serum with bacterial endotoxin generated a new serum factor (M.W. 60,000) which results in histamine release. This mechanism probably involves a humoral immune reaction resulting in the production of a complement component or fragment which reacts with receptors on mast cells to release histamine. In addition, some substances which are mitogenic for T cells have also been found to release histamine.

Finally, Mrs. J. Phillips and Dr. S. Mergenhagen have just concluded elegant studies indicating that minute quantities of "natural" $\gamma 2$ antibodies in guinea pig and man are responsible for the activation of the complement sequence by endotoxins. The resultant inflammatory reaction to this antigen can therefore ensue in the absence of purposeful immunization, since low levels of environmental exposure to the antigen results in enough antibody to activate the complement cascade in the usual fashion.

Dr. H. Kirchner plans to study the relationship of B and T cell interactions in chickens to production of mediators of cellular immunity and tumor immunity. In allergic humans we plan to study the efficacy of types of hyposensitization therapy in producing blocking antibodies. This will hopefully also help us in evaluating this type of approach in prolongation of graft survival in man. We hope that further improvements in extraction of soluble histocompatibility antigens and their purification will provide us with material that has tolerogenic effects.

We have elicited contract proposals from nearby commercial scientific enterprises to study the nature of the antigens in plaque which are responsible for lymphocyte activation. We also plan to investigate the mediators produced by such lymphocytes. Increased understanding may lead to improved means of reducing plaque-induced periodontal inflammation.

Finally, our Section will be joined on July 1, 1972 by Dr. D. Rosenstreich, who will pursue studies of macrophage-lymphocyte interactions, and by Dr. Ann Sandberg, whose immunochemical expertise will aid us to pursue studies of complement and humoral factors in immune inflammation.

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Report of the Virology Section
National Institute of Dental Research
Summary Statement*

The ability of viruses to replicate in cells and interfere with the normal physiology of the cell has long been considered the major cause of viral pathology. The immune response to viral infections is thought to protect the host by neutralizing infectious particles and by eliminating virus-infected cells. Evidence is beginning to accumulate, however, which indicates that the immune response to viral infections may not always be beneficial to the host, and in fact may contribute to the pathology of certain viral diseases.

For a number of years the Virology Section has been interested in the immune response to viral infections and the various factors which can initiate immunopathologic changes. These factors can be divided into 5 categories or mechanisms (Table I).

Mechanisms of Virus-Induced Immunopathology

Mechanisms		Pathology
I)	Formation of Circulating Virus-Antibody Complexes	Immune Complex Disease
II)	Interaction of (a) Antiviral Antibody plus Complement or (b) Immune Cells with Virus-Induced Cell Surface Antigens	Destruction of Infected Cells
III)	Virus-Induced Activation of Biological Mediators from (a) Complement or (b) Immune Lymphocytes	Inflammation, Allergic Reactions, Destruction of Cells
IV)	Immune Response to Host Cell Antigens that have been Unmasked, Altered or Derepressed by Virus	Autoimmune Reactions
V)	Infection of Immune System	Immunological Derangements

* This report is based upon progress achieved during the year in Project Nos. NIDR-LMI-72-015-(b)-(67), NIDR-LMI-72-016-(b)-(71), NIDR-LMI-72-017-(b)-(70), and NIDR-LMI-72-018-(b)-(71).

First, the immune response of the host to viral antigens may result in the formation of circulating virus-antibody complexes, which can in turn react with a variety of humoral agents, including anti-immunoglobulins, the components of complement, or rheumatoid factor. Moreover, it is recognized that deposition of these virus-antibody complexes in the kidneys can lead to the development of immune-complex glomerulonephritis. Second, viruses can induce new antigens on the surface of infected cells, and the interaction with immune lymphocytes or specific antiviral antibody plus complement can result in cell destruction. Third, the release of activation of biological mediators from immune lymphocytes or from the components of complement can result in inflammation, allergic reactions and cell damage. Fourth, the immune response to host cell antigens that have been unmasked, altered or derepressed by the virus might lead to autoimmune disease. Fifth, viruses can infect the cells of the immune system and thereby produce immunologic derangements. This latter mechanism may be extremely important in the persistence of certain viral infections, and in the initiation and potentiation of tumors. In previous reports we have directed our attention to Mechanisms I, III and V. This year we will describe our findings on Mechanism II.

In its first phase, this work concerned the detection of viral antigens on the surface of infected cells. Although immunofluorescence has been widely used for this purpose, this technique is difficult to quantitate and interpretations are subjective. To overcome some of these difficulties we labeled antibody against herpes simplex virus (HSV) with ^{125}I instead of fluorescein. Our experiments showed that the ^{125}I-labeled antibody bound specifically to HSV infected cells, and that this was a highly sensitive, rapid, and objective method for detecting newly synthesized viral antigens and for determining the time of appearance of these antigens on the surface of infected cells. Moreover, incubation of infected cells with unlabeled antiviral antibody specifically blocked the attachment of ^{125}I-labeled antiviral antibody, and by this inhibition technique the titer of the unlabeled antiviral antibody in a particular serum could be determined.

Recently, an even simplier approach for detecting antiviral antibody has been developed. Cells were infected with HSV and then incubated with unlabeled anti-HSV. ^{125}I-labeled anti-gamma globulin then was added and the amount of ^{125}I bound to the antiviral immunoglobulin on the surface of the infected cells was determined. Our experiments showed that the binding of ^{125}I-labeled anti-gamma globulin to the surface of HSV-infected cells was directly related to the concentration of anti-HSV antibody that had attached to the cells. This indirect technique has the advantage of employing a single isotopically labeled reagent (e.g. ^{125}I-labeled anti-human gamma globulin) in the detection of antibody (e.g., human) against different viruses. Moreover, because of the amplification step involved in the attachment of anti-gamma globulin to antiviral immunoglobulins, this indirect technique is highly sensitive. Preliminary experiments suggest that it is 100 to 1000 times more sensitive than the commonly used complement fixation test. Antibody titers greater than 100,000 have been detected.

The major disadvantage of both the direct and indirect techniques is the requirement for fairly large quantities of materials and a monolayer of viable cells. During recent months we have developed an indirect micro-radioimmunoassay which requires only small amounts of material (25μl), and employs soluble antigens prepared from a lysate of infected cells. In brief, we found that viral antigens adhered to the surface of polyvinyl wells (microplates containing 96 wells). Unlabeled antiviral antibody bound specifically to the adherent viral antigens. As in the case described above, by measuring the subsequent attachment of ^{125}I-labeled anti-gamma globulin to the unlabeled antiviral antibody, the titer of the unlabeled antiviral antibody could be determined. In addition to the advantage of employing minute amounts of material and soluble viral antigens, this procedure is technically simple and extremely rapid. Moreover, the 96 wells on the plate can be washed (at the appropriate times in the procedure) as a single unit rather than as 96 separate tubes. Consequently, this part of the procedure requires only a few seconds. In addition, samples can be quantitated in an automated gamma counter and data transmitted directly to a computer, where antibody titers can be calculated and recorded. Thus, the indirect micro-radioimmunoassay appears to be a practical and highly sensitive technique for measuring anti-viral antibody and could prove useful in both research and clinical laboratories.

The second phase of our work has been concerned with the biological significance of these virus-induced cell-surface antigens. Our experiments showed that the interaction of specific antiviral antibody and complement with these antigens resulted in cell destruction which could be quantitated by the release of ^{51}Cr from the injured cells. We found that a number of factors could influence the degree of cell destruction, including the density of viral antigens on the surface of infected cells and the nature of the anti-viral antibody. Although it has been speculated by a number of investigators that immunological injury may contribute to the pathology of certain viral infections, it has been difficult to dissect and evaluate this phenomenon *in vivo*. Our studies indicate that the release of ^{51}Cr from virus-infected cells by antiviral antibody and complement offers a simple, objective, and quantitative technique for studying immunological injury *in vitro*. By use of this technique it should be possible to study different viruses and to evaluate the role of cytolytic versus noncytolytic antiviral antibody in the serum of patients during the course of different viral infections.

It should be stressed, however, that immunologically-mediated destruction of virus-infected cells may have beneficial as well as deleterious effects on the host. The recognition of viral antigens on the surface of infected cells by antiviral antibody and the destruction of these cells by complement provides the host with a highly specific, rapid, and potentially effective defense mechanism. The immunological destruction of virus-infected cells would shut off virus replication and release or expose the infectious virus within the cells to neutralizing antibody. In addition, antibody-mediated destruction of virus-infected cells may be one of the mechanisms by which the host combats those viruses (e.g. HSV) which, by spreading directly from cell to cell avoid neutralization. Thus, in viral infections, antibody-mediated cell destruction may supplement the role that has been postulated for cellular immunity.

The third phase of our work is concerned with the cellular immune response to viral infections. Although it is thought that cell-mediated immunity plays an important role in the defense against certain viral infections, its precise role has been difficult to assess because of the lack of a simple in vitro assay. Over the last year we have developed an in vitro assay, based on the observation that lymphocytes from viral immunized animals can be stimulated in vitro by specific viral antigens (as measured by the incorporation of ^{3}H-thymidine into acid insoluble material). For example, lymphocytes from animals immunized with HSV can be stimulated by HSV, but not by vaccinia. Conversely, lymphocytes from animals immunized with vaccinia can be stimulated by vaccinia, but not by HSV. In addition, this in vitro technique makes it impossible to determine the time of appearance, duration, and magnitude of the cellular immune response following infection.

The role of the cellular versus the humoral immune response in viral infections and the relationship between these two responses has been the subject of considerable speculation. By use of the in vitro lymphocyte stimulation technique we have begun to study this problem. Preliminary experiments indicate that concentrations of anti-HSV antibody that were capable of neutralizing 100% of the infectious virus had no inhibitory effect on the ability of HSV antigens to stimulate immune lymphocytes. If the ability of HSV-anti-HSV complexes to stimulate immune lymphocytes can be confirmed with other viruses, this would suggest that the host has evolved a highly effective way of protecting the cells of the immune system from destruction by infectious virus, while at the same time allowing viral antigens to stimulate the immune system. In this way, the humoral and cellular immune responses may work in conjunction to combat viral infections.

There are several mechanisms by which cell-mediated immunity might defend the host against viral infections. Immune lymphocytes might react with and destroy virus-infected cells by processes similar to those involved in the cell-mediated destruction of tumors and grafts. Moreover, the release of lymphotoxin, migration inhibitory factor, chemotactic factors, interferon and other biological mediators from stimulated lymphocytes might inhibit viral replication and lead to the destruction of virus-infected cells. Thus, on the one hand, the cellular immune response may aid in the defense against viral infections, while on the other hand the immunological destruction of virus-infected cells may contribute to the pathological manifestations of the infection.

Experiments on various aspects of Mechanism II (described above) will be continued and expanded. Attempts will be made to apply some of our new information and techniques to selected clinical problems. In addition, experiments will be initiated on Mechanism IV. Additionally, when space and personnel are made available we will initiate a new project to investigate the very real possibility that viruses are involved in the etiology of aphthous ulcers and other soft tissue lesions (e.g., tumors and salivary gland disease) of the oral cavity.

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Report of the Dental Services Branch
National Institute of Dental Research
Summary Statement

The Dental Services Branch provides collaborative clinical support to all NIDR intramural programs and extends necessary dental care to the NIH-wide research patient population at the Clinical Center. The Dental Clinical Associate program offers career development opportunities to young clinicians who have research interests.

Intramural Support and Clinical Programs:

The Branch contributes to intramural programs directly and through collaborative activities with other units of the Institute as follows:

Caries - A study of differences in occurrence of dental caries in Caucasian and Negro children is under investigation. Differences in enamel fluorosis between these two groups is being studied.[1]

Dental Materials - A collaborative study with the National Bureau of Standards has been initiated to study the effects of the gamma 2 phase on the physical properties of dental amalgam.[2]

Sjögren's Syndrome - Lower lip biopsies are taken of patients with Sjögren's syndrome for the purpose of radio-immunoelectrophoretic and histologic studies to evaluate for lymphoid infiltration and synthesis of immunoglobulins.[3]

Tissue Healing - Post-operative stability of the dental occlusion and the temporomandibular joints of patients following various techniques of maxillary or mandibular osteotomy continues under study.[4] Factors associated with the development of post-extraction localized osteitis are also being studied.[5]

Tooth Transplantation Study - Currently active NIDR patients who have available siblings have been screened and tested for tissue compatibility for the purpose of identifying compatible pairs for tooth transplantation. To date, several compatible sibling pairs have been identified and a transplant undertaken.[6]

Inter-Institute Collaborative Services:

The Branch provides dental services to the clinical programs of all the categorical Institutes.[7] The following examples are cited:

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1. NIDR-DS-72-002-(c)(68)
2. NIDR-DS-72-006-(a)(72)
3. NIDR-OMS-72-008-(c)(72)
4. NIDR-DS-72-005-(c)(67)
5. NIDR-DS-72-004-(c)(67)
6. NIDR-OMS-72-011-(c)(72)
7. NIDR-DS-72-001-(c)(72)

National Heart and Lung Institute - The Branch heavily supports the clinical programs of the NHLI Cardiology and Surgery Branches. Cardiac surgical candidates with congenital or acquired heart defects who require a cardio-vascular prosthesis are provided comprehensive dental care to control the oral environment as a focus of postoperative bacteremias.

National Cancer Institute - Excellent liaison with the NCI Surgery Branch continues. Our prosthetic and oral surgery services receive an increasing number of consultations to aid in the management of head and neck oncologic surgical cases. Dental evaluation at the critical preoperative workup of these patients has come to be appreciated by the NCI staff.

National Institute of Arthritis and Metabolic Diseases - Submaxillary saliva is collected for the purpose of immunologic and biochemical studies of the products of accessible secretory glands such as salivary glands in patients with cystic fibrosis.

Dental Clinical Associateship Program:

This program offers a combination of research and clinical opportunities to the young clinicians of the Dental Services Branch. During the past year, Branch Clinical Associates have been collaborating with various laboratories on the following projects:

Study of dentoalveolar pathology in human skulls.
Epidemiology Section
Disease Prevention and Therapeutics Branch, NIDR

Histochemical studies of the rat gingiva.
Histochemistry Section
Experimental Pathology Branch, NIDR

Studies of tooth transplantation and implantation.
Oral Medicine and Surgery Branch, NIDR

Gamma 2 phase in dental amalgams.
Research Division, American Dental Association
National Bureau of Standards, Department of Commerce

Report of the Oral Medicine and Surgery Branch
National Institute of Dental Research
Summary Statement

The diversity of the program of the Oral Medicine and Surgery Branch is exemplified in the research projects of the eight investigators included in this summary. The projects are arbitrarily grouped under the following headings and will be discussed in this same sequence: (1) Connective tissue diseases, (2) Salivary studies, (3) Allogeneic tooth transplantation, (4) Oral area motor mechanisms and oral-facial tissue hemodynamics, (5) Oncology, and (6) Roentgenography.

Connective Tissue Diseases

Sjögren's Syndrome.[1] The preponderance of studies of the Branch relate to Sjögren's syndrome, an autoimmune connective tissue disease. Because this syndrome involves so many facets of disease - the immune system, connective tissues, salivary glands, mucosal manifestations, and caries - it is viewed as a model for the study of a wide range of oral conditions. Additionally, because the autoimmune diseases, Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, etc., are still so poorly understood, a greatly increased share of attention has been placed upon this group in the fiscal year 1972. During the year, important findings have been made by this group of investigators. In animal studies, immune complexes consisting of nucleic acids (Primarily DNA) were demonstrated in vivo in the reticulo-endothelial system of the New Zealand Black mouse which spontaneously develops both Sjögren's syndrome and lupus erythematosus.[2]

This finding supports the concept that an autoimmune mechanism is involved in the etiology of Sjögren's syndrome and lupus erythematosus.

By means of immunochemical studies in patients with Sjögren's syndrome, a local synthesis of IgM anti-antibodies and rheumatoid factor by oral labial mucosal tissue culture was demonstrated. The IgM and rheumatoid factor may be related to the seriousness of the disease, and clinical improvement on immunosuppressive drugs is related to a decrease of these substances. A quantitative technic to show the presence of anti-salivary duct antibody in patient's sera has been developed. Utilizing radioactive tagged IgG (anti-salivary duct antibody) in sera, a method for the isolation and identification of the salivary gland antigens responsible for the production of this antibody is available.

Some patients with Sjögren's syndrome have cryoglobulinemia. A new technic for the isolation and purification of the Fd or Fd' fragment from human

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[1] NIDR-OMS-72-008-(c)-(72)

[2] NIDR-OMS-72-004-(c)-(72)

myeloma IgG cryoglobulin was developed.[3] This technic will allow further study of the autoimmune mechanism which may underlie Sjögren's syndrome.

Behcet's Syndrome.[4] Behcet's syndrome is a connective tissue disease which involves the oral cavity among other organs and tissues. First described in 1937, little is yet known of the etiology, pathogenesis, or even of the natural history of this syndrome. The syndrome consists of aphthous stomatitis, genital ulcers, eye inflammation and a variety of other vascular and inflammatory components such as arthritis, brain vasculitis, skin lesions and gastrointestinal ulcerations. A study of patients with Behcet's syndrome has revealed three important aspects of the disease: (1) brain involvement may be far more common than previously suspected, and may be asymptomatic in some, (2) mortality for central nervous system disease may be lower than the reported figures of a 10% frequency with 50% mortality during the first year, and (3) judicious tapering of corticosteroid dosage is a viable goal, even in patients with severe brain involvement. A broader view of the various oral manifestations in this systemic connective tissue disease was achieved. A rational classification apropos to diagnosis and therapy has been devised based on the oral manifestations in systemic connective tissue disease.

Salivary Studies

Salivary studies related to Sjögren's syndrome.[5] Parotid saliva from Sjögren's patients was studied by means of paper electrophoresis. The electrophoretic and documentation systems for salivary proteins in patients with this disease have been developed. Results show protein patterns differing from those in normal controls. The greater resolving power of the polyacrylamide gel protein electrophoresis will be utilized to study saliva from Sjögren's syndrome patients to further elucidate the protein patterns.

Human body fluid isoamylases.[6]

A. Salivary isoamylase genetics. In a study population of 183 twin pairs, in collaboration with Dr. J. T. Schwartz, NEI, a strong indication was found that the so-called "C-2" band was genetically controlled. A complete family evaluation on each of the families containing a positive twin pair is scheduled.

B. Pleural fluid isoamylases. A collaborative study with Dr. Howard Sherr, Johns Hopkins School of Medicine, investigating the isoamylases of pleural fluid has been started and the first paper originating from it, entitled "Origin of Pleural Fluid Amylase in Esophageal Rupture," has been accepted for publication. This paper describes a case of esophageal rupture with a

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[3] NIDR-OMS-72-007-(c)-(68)

[4] NIDR-OMS-72-009-(c)-(68)

[5] NIDR-OMS-72-018-(c)-(72)

[6] NIDR-OMS-72-019-(c)-(72)

high pleural fluid amylase. By means of the polyacrylamide gel electrophoresis method it was shown that the pleural amylase was salivary rather than pancreatic in origin (reflux of intestinal juices). The next endeavor in this study is an analysis of pleural fluid samples from patients with thoracic tumors, using the above method of identifying pancreatic and salivary isoamylases in body fluids.

Functional salivary gland studies. Investigation of major salivary duct obstruction by sequential salivary scintigraphy showed atypical Tc^{99m}-pertechnetate uptake in parotid glands. While not of itself surprising, this observation lends support to the notion that pertechnetate scintigraphy will be most useful in determining the exact stage at which salivary gland dysfunction occurs in diseases affecting the major salivary glands. Fuller exploitation of this technique in clinical diagnosis will be undertaken in the course of present and projected studies which involve assessment of salivary gland function.

Allogeneic Tooth Transplantation[7]

The tooth transplantation project was developed for implementation at the beginning of the fiscal year 1972. This project involves histocompatibility and ABO blood group antigen matching of donor and recipient prior to transplantation, and immunologic monitoring of the recipient for rejection phenomena following transplantation. Immunosuppressive drugs are not being used following transplantation in this project.

The initial transplantation procedure between a donor and a recipient matched with respect to their histocompatibility and ABO blood group antigens was done on January 31, 1972. Clinical examination and mixed lymphocyte cultures have not revealed any evidence of rejection of the transplant during the four month postoperative period. Continued examinations will be done at monthly intervals for 3 to 5 years. Additional donor-recipient pairs have now been matched for transplants to be performed during the coming months.

In parallel with the transplantation project, a long-term study of the implantation of non-natural materials, principally porous calcium aluminate ceramic, as a replacement for lost teeth is being conducted.[8] Fifteen porous ceramic implants and 4 porous titanium implants have been placed in fresh extraction sites in Rhesus monkeys. Implants of modified design will be placed in the coming year in an effort to define the potential of dental implantation.

Oral Area Motor Mechanisms and Tissue Hemodynamics

Form and Function of the oral-facial tissues have been studied in two related projects.

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[7] NIDR-OMS-72-011-(c)-(72)

[8] NIDR-OMS-72-010-(c)-(70)

A. Studies of oral area motor mechanisms by use of displacement and pressure transducers.[9] There was a successful attempt at modification of velar movement (elevation at the velum) during speech tasks using a previously developed displacement transducer. A dual-beam force transducer was developed to measure intraoral forces. This instrument has been used to measure the passive bilateral forces of the tongue at various degrees of lingual width or constriction. Data on seven subjects revealed that passive lingual pressure against the teeth is of very low magnitude (< 0.5 g/mm^2).

Electronic dynamometers were developed to measure oral biting forces. These instruments will be used to study values of biting force in normal subjects at various degrees of mandibular elevation, and lateral and protrusive displacements. Data will be collected on patients with disorders of temporomandibular joint and neuromuscular dysfunction.

B. Hemodynamics of oral-facial tissues.[10] A system was previously developed to control blood perfusion to the mandible and to the mandibular teeth. Catecholamines and serotonin produced a 25% increase and histamine a 15% decrease in vascular resistance to mandibular blood flow.

Oncology

Odontogenic tumors.[11] A previous publication has described odontogenic growths consisting primarily of osteocementum which occurred in aged hamsters that had been infected with Rat Virus (RV) at 5 days of age. It was the purpose of this investigation to determine whether Minute Virus of Mice (MVM) would initiate odontogenic growths or tumors. Odontogenic growths, histologically consistent with cementomas, and, in one case, an odontoma, occurred in aged hamsters infected with MVM at 5 days of age. Odontogenic growths occurred in the mandibles of all experimental animals but not in the control animals.

Roentgenography[12,13]

It has been shown that the ability to diagnose caries from radiographs is strongly influenced by the way the information is presented. Specific results suggest that the mode of display is far more important than a substantial loss of channel capacity resulting from either loss of resolution and grey level range, or the presence of appreciable film fogging produced

[9] NIDR-OMS-72-003-(c)-(65)

[10] NIDR-OMS-72-002-(c)-(70)

[11] NIDR-OMS-72-001-(c)-(72)

[12] NIDR-OMS-72-016-(c)-(72)

[13] NIDR-OMS-72-017-(c)-(72)

by extraneous radiation. These findings also show that certain modes of display result in significant reductions in the number of diagnostic errors produced by unbiased interpretation of dental radiographs containing known pathology. The results were found to be consistent with heuristic guidelines developed as a part of the research to provide a basis for selecting perceptually meaningful modes of information display. Of current interest is the degree to which these guidelines can be formalized and the extent to which they are applicable to other perceptual tasks of diagnostic interest. These activities take precedence over empirical methods for optimizing preprocessing techniques since the number of alternatives is far too great to permit comprehensive survey and evaluation.

Current efforts have been conducted in two directions:

A. Basic research designed to limit the domain of promising techniques for preprocessing visual information. Specific experiments have been performed which demonstrate that the human visual system can easily recognize first order spatial redundancy manifest in three as well as two dimensions.

B. Applied research to demonstrate the degree to which proven preprocessing techniques are applicable to a variety of diagnostic tasks. The most ambitious project of an applied nature involves the design of a completely new type of dental radiographic system. This system couples an intraoral source of radiation to an extraoral transducer. The output of the device is an "on line" preprocessed visual display which can be stored both photographically and electronically.

Report of the Oral and Pharyngeal Development Section
Oral Medicine and Surgery Branch
National Institute of Dental Research
Summary Statement

The activities of this Section continue to be concerned dually with the development of structure and the development of function in the oral and pharyngeal area. Our continuing presumption is that anatomical and physiological development are integrally related. Evidences of this integration are accumulating, from our own work and that of a variety of other investigators of development.

Most of our current studies are of newborn human infants, or term fetuses. Some studies extend into earlier or later developmental comparisons or into homologic developmental comparisons. Most of our clinical work with anomalous or neurologically impaired persons consists of accumulation of exemplary patients whose oropharyngeal defects are assessed by procedures which are standard within the Section.

With respect to ongoing sectional activities relating to structure, this is the third year of gross anatomical studies of the face, pharynx and cranium of the human fetus at term. We are now engaged in illustration, writing and initial publications. Thirty-two aspects of the dissected fetal head have been illustrated by Howard Bartner, while an additional nine drawings of coronally sectioned fetal heads have been prepared by Keiko Moore. Twenty-six of these dissection illustrations were included in a preliminary anatomical description of the region, which will appear in the proceedings of the Third Symposium on Oral Sensation and Perception: The Mouth of the Infant, now in press.[1] These illustrations, and others now in design, will ultimately provide the basis for a detailed anatomical atlas of the fetal head.

In a related study, Mrs. Moore completed a lengthy series of illustrations describing the fetal skull, including not only its general aspects but also its detailed morphology in coronal and transverse sections. Each of the anatomical sections matches a tomoradiograph. This material is now in final stage of preparation as an Atlas of Cranial Anatomical Sections and Tomoradiographs of the Human Fetus at Term, authored by Robert Pierce (former Associate in Radiology at the Clinical Center), Michael Mainen (former Clinical Associate in this Section), and James Bosma.[2]

Nineteen of a total of approximately forty illustrations of selected areas of term fetal crania and of individual bones have now been completed by Beverly Etter. These, supplemented by fractions of the section illustrations noted above and a small number of radiographs and detail photographs, comprise the material of a prospective general book, The Head Skeleton of the Human Fetus at Term, by J. Bosma. These two descriptions of the human fetal head skeleton correspond in approach and in demonstration with the book, Development of the

1. NIDR-OPD-72-001-(c)(72)
2. NIDR-OPD-72-003-(c)(72)

Rat Skull, by Melvyn Baer, James Bosma, and James Ackerman, the pending publication of which is a collaborative project of the NIDR and the National Library of Medicine.

Detailed anatomical studies of the "pars villosa" of the lip are in progress by Dr. Bradley Thach.[3] This villous organ is an anatomically peculiar intersection of capillary loops, nerves and labial mucosa which is developmentally transient in the human fetus and neonate. Dr. Thach is engaged in broadly designed histological studies, including the preparation of schematic representations of the vascular loops, special stains for neural networks, and histochemical studies of epithelial cells. The study is developmental, in the human fetus and infant. It is also homologic, comparing possibly similar structures in fetuses and sucklings of other mammals.

The normative and clinical studies of function in the oral and pharyngeal area of human infants and children are graduating in approach. Until recent years, we had recorded only the motions of feeding, respiration and vocalization or speech. Our observational concerns and questions are now directed toward the sensory evocation and guidance of these motor functions, and toward the variety of subjective experiences and responses which oral sensations elicit. Some parameters of our work, such as intensity or site of touch, as single versus two-point touch, or the concentration of various tastants, are concerned specifically with sensory performance. Other procedures, such as approximation of tongue to discontiguous touch sites, or tongue following of a contiguous touch cue, or oral recognition of stereognosis forms, utilize tactual cues to evoke and guide motor function.

In this latter category, i.e., sensory cuing of motor response, Dr. James Weiffenbach discovered and initially standardized a reflex-like response of ipsilateralward motion of the tongue tip upon touch stimulation of the lingual lateral margin.[4] This study was originally described under the titles, "Discrete Elicited Motions of the Newborn's Tongue" and "Infants with Clefts of Lip and Palate: Observations of Touch Elicited Oral Behavior" at the Third Symposium on Oral Sensation and Perception, and will shortly appear in the Symposium volume. Subsequently, Doctors Weiffenbach and Thach have further calibrated this response, and have now extended their studies both by inclusion of premature infants in the panel, and also by the introduction of measured microvolumes of tastants as an alternative mode of stimulation. The methodology of observation has also been expanded by the use of infrared video recording.

The tongue response is found to be varied in modality of elicitation, consistent in site of elicitation and in motions of response, and stable within the range of response states of the term born neonate. It is now apparent that this response is a strategic addition to our sensorimotor examination of the infant.

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3. NIDR-OPD-72-002-(c)(72)
4. NIDR-OPD-004-(c)(71)

These intramural activities of the Section have continued in integration with the design, arrangement and publication of the Symposia on Oral Sensation and Perception. The Third Symposium, subtitled: The Mouth of the Infant, was held under joint NIDR-Fogarty International Center sponsorship November 23-25, 1970, and will be published in the summer of 1972 by C. C. Thomas.

The Fourth Symposium, subtitled: Development in Infancy, is scheduled for November 1972. Its roster is completed and its agenda currently being arranged. There has been a notable graduation in modus operandi of these Symposia. The first and second Symposia consisted of an assortment of presentations of material developed in varied contexts, but assembled in relation to the Symposium theme. Their original and significant contribution was that of topical focussing and of the interactions of the participants. On the occasion of the Third Symposium, however, it became apparent that substantially more of the presentations described studies either devised consequent to the influence of the earlier Symposia, or, at the very least, were couched in a context directly relating to them. In addition to their evident catalytic role in stimulating investigative interest, the Symposia also appear to have served as very effective environments for scientific exchange in a topical area heretofore lacking an adequate forum.

NIDR ANNUAL REPORT - FY 72

RESEARCH PROJECTS AND INDEXES

INTRODUCTION

Aside from the usual function of indexes -- that of guiding the reader from an isolated bit of information to the whole -- the ones in this Report provide several different views of the research activities within the National Institute of Dental Research. All of the basic information elements from each reported project were stored in a WYLBUR data set and selectively retrieved in alphabetical or numerical order. The format varies somewhat due to the lack of time which prevented the usual testing and proofing of each program.

In regard to the Index of Research Projects by Subject Areas, the reporting investigators were asked to underline about five keywords (without regard to category) and to double-underline the single most significant keyword in their project report. These terms were then converted, when necessary, to conform with those found in the National Library of Medicine' published vocabulary, Medical Subject Headings (MeSH), and are printed in upper-case letters. Non-MeSH keywords used by the investigators to describe their projects are printed in upper- and lower-case letters. These terms are then cross-referenced in our Report to the nearest comparable MeSH term.

Following each of the major subject area word or group of words is a letter enclosed in parenthesis which denotes one of six categories important to the analysis of research at NIDR. They are:

(A) Diseases and Disorders
(B) Fields of Science and Related Subjects
(C) Technics and Equipment
(D) Biomaterials, Chemicals and Drugs
(E) Anatomical Terms
(F) Organisms and Named Groups of People

A complete list of the Categories and the terms in each from the last two Annual Reports will be found following the Indexes in this section (Blue).

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(1) As determined by the Principal Investigator for the Project

(2) P - Principal Investigator
C - Co-Principal Investigator

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RESEARCH PROJECTS BY SUBJECT AREAS

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RESEARCH PROJECTS BY TYPE OF RESEARCH

* As defined by the Principal Investigator

Category A

DISEASES AND DISORDERS

AMLOIDOSIS
AUTOIMMUNE DISEASES
BEHCET'S SYNDROME
CARCINOMA
CARIES, DENTAL
CARIES, ROOT
CLEFTS
CONNECTIVE TISSUE DISEASES
DEAFNESS
DENTAL CALCULUS
DENTAL CARIES
DENTAL PLAQUE
DIABETES MELLITUS
ENDOCRINE DISEASES
ETIOLOGY
FLUOROSIS
GENETIC DISORDERS
GINGIVAL HYPERPLASIA
GINGIVITIS
HEREDITARY DISEASES
HYPERPLASIA
INFLAMMATION
KERATOSIS
LEUKEMIA
LEUKOEDEMA
MALFORMATIONS
MALOCCLUSION
METABOLIC DISEASES
NEOPLASMS
ODONTOGENIC TUMOR
OSTEITIS
PAIN
PERIODONTAL DISEASES
PRECANCEROUS CONDITIONS
PSEUDOHYPOPARATHYROIDISM
ROOT CARIES
SARCOIDOSIS
SJOGREN'S SYNDROME
STOMATITIS, APHTHOUS
SUBMUCOUS FIBROSIS
TERATOID TUMOR
TRIGEMINAL NEURALGIA
VIRUS DISEASES

Category B

FIELDS OF SCIENCE AND RELATED SUBJECTS

AGING
AMINO ACID SEQUENCE
ANATOMY
ANESTHESIOLOGY
ANTHROPOLOGY
ANTIBODY FORMATION
BIOCHEMISTRY
BIOLOGY
BIOMEDICAL ENGINEERING
BIOPHYSICS
BLOOD COAGULATION
CELL DIVISION
CHEMISTRY
CHEMISTRY, PHYSICAL
CHEMISTRY, PROTEIN
CHEMOTAXIS
COAGULATION
COMPUTER SCIENCE
CRYSTALLIZATION
CYTOLOGY
DELIVERY OF HEALTH CARE
DENTAL OCCLUSION
DENTISTRY, PREVENTIVE
DEVELOPMENT
DISCRIMINATION
ELECTROPHORESIS, DISK
ELECTRON SPIN RESONANCE
EMBRYOLOGY
ENZYMOLOGY
EPIDEMIOLOGY
EVOLUTION
FERMENTATION
GENETICS
GRAFT VS HOST REACTION
GROWTH
HEMODYNAMICS
HEURISTICS
HISTAMINE LIBERATION
HISTOCHEMISTRY
HISTOCOMPATIBILITY
HISTOLOGY
HISTOPATHOLOGY
IMMUNITY
IMMUNOCHEMISTRY
IMMUNOLOGY
INHIBITION
MEDICINE
METABOLISM
MICROBIOLOGY
MOTOR ACTIVITY
NEUROLOGY
NEUROPHYSIOLOGY
NUTRITION
ODORS
ORTHODONTICS
PATHOLOGY
PERCEPTION
PERIODONTICS
PHARMACOLOGY
PHYSIOLOGY
RHEUMATOLOGY
SENSATION
SPEECH
STOMATOLOGY
SURGERY, ORAL
TASTE
TERATOLOGY
VIROLOGY
WOUND HEALING
ZOOLOGY

Category C

TECHNICS AND EQUIPMENT

ANALYSIS
ANESTHESIA
ANTIGEN-ANTIBODY REACTIONS
ATLASES
AUTOANALYSIS
AUTOMATION
BACTERIOLOGY
BIOCHEMISTRY
BIOMETRY
BIOPSY
BIOSYNTHESIS
CANNULATION
CEPHALOMETRY
CHARACTERIZATION
CHEMISTRY
CHROMATOGRAPHY
CHROMATOGRAPHY, GAS
CLASSIFICATION
COMPLEMENT FIXATION TESTS
COMPUTERS
CYTOCHEMISTRY
CYTODIAGNOSIS
DEMOGRAPHY
DENSITOMETRY
DENTAL IMPLANTATION
DENTAL PROPHYLAXIS
DIAGNOSIS
DIET
DISSECTION
DMF INDEX
DRUG THERAPY
ELECTROCARDIOGRAPHY
ELECTROENCEPHALOGRAPHY
EXAMINATION
EXODONTIA
FLOW RATES
FLUORESCENT ANTIBODY TECHNIC
FLUORIDATION
FLUOROMETRY
FREEZE-ETCHING
HEMODYNAMICS
HISTAMINE LIBERATION
HISTOCOMPATIBILITY TESTING
HISTOLOGICAL TECHNICS
HYPERSENSITIVITY
IMMUNOASSAY
IMPLANTATION
INFORMATION RETRIEVAL SYSTEMS
LYMPHOCYTE TRANSFORMATION
MEDICAL ILLUSTRATION
MICROINCINERATION
MICROSCOPY
MICROSCOPY, ELECTRON
MICROSCOPY, FLUORESCENCE
MODELS, THEORETICAL
MOTION PICTURES
OSTEOTOMY
PERFUSION
PHOTOGRAPHY
PHYSICS
POLYGRAPH
PRECIPITATION
PSYCHIATRIC CONSULTATION
PURIFICATION
RADIOAUTOGRAPHY
RADIOGRAPHY
RADIOGRAPHY, DENTAL
RADIOIMMUNOASSAY
SCINTILLATION
SPECTROPHOTOMETRY
SPECTRUM ANALYSIS
STATISTICS
STEREOGNOSIS
SURGERY
TACTILE STIMULATION
THERAPEUTICS
TOMOGRAPHY
TONGUE TRACKING
TRANSDUCER
TRANSPLANTATION
VACCINATION
X-RAY DIFFRACTION

Category D

BIOMATERIALS, CHEMICALS, AND DRUGS

ADHESIVE SEALANTS
AGAR
AMINO ACIDS
AMYLASE
AMYLOID
ANTIBODIES
ANTIGENS
ANTIHISTAMINICS
ANTI-INFECTIVE AGENTS
ANTIMICROBIAL
ANTISEROTONIN
ANTITHYMOCYTE SERUM
APATITES
CALCIUM PHOSPHATES
CARBOHYDRATES
CARCINOGENS
CERAMICS
COMPLEMENT
COLLAGEN
CORTICOSTERONE
CRYOGLOBULINS
DENTAL AMALGAM
DEXTRAN
ELECTROLYTES
ENDOTOXINS
ENZYMES
FLUORIDES
FOLIC ACID
GAMMA GLOBULIN
HORMONES
HYDROXYAPATITE
IMMUNE SERUMS
IONS
LECITHINS
METALS
MOUTHWASHES
MUCOPOLYSACCHARIDES
PEPTIDES
PHOSPHATES
PHOSPHOLIPIDS
POLYSACCHARIDES
PROTEINS
RNA
STEROIDS
SUCROSE
TABLETS
TERATOGENS
TETRACYCLINE
TISSUE FACTOR
TOOTH, ARTIFICIAL
ZIRCONIUM

Category E

ANATOMICAL TERMS

AMELOBLASTS
AMNIOTIC FLUID
BLOOD
BONE AND BONES
CARTILAGE
CENTRAL NERVOUS SYSTEM
CHEMORECEPTORS
CHICK EMBRYO
CONNECTIVE TISSUE
DENTAL ENAMEL
DENTAL PULP
DENTIN
DENTITION
EMBRYO
ENZYMES
FACE
FACE, EMBRYONIC
FETUS
GENITALIA
GINGIVA
HAIR
HEAD
INTERCELLULAR JUNCTIONS
JAW
LEUKOCYTES
LIP
LYMPHOCYTES
LYSOSOMES
MACROPHAGES
MANDIBLE
MAST CELLS
MONOCYTES
MOUTH
MOUTH MUCOSA
MUSCLE
NEWBORN
PALATE
PERIODONTIUM
PERIPHERAL NERVOUS SYSTEM
PHARYNX
PLEURAL FLUID
RIBOSOMES
SALIVA
SALIVARY GLANDS
SKULL
SPLEEN
SYNAPSES
TEMPOROMANDIBULAR JOINT
TENDONS
THYMUS GLAND
TISSUE, CONNECTIVE
TISSUE, DIFFERENTIATING
TISSUE, MINERALIZED
TONGUE
TOOTH
TRIGEMINAL NERVE
VELUM

Category F

ORGANISMS AND NAMED GROUPS OF PEOPLE

BACTERIA
CHICKENS
CHILD
CLINICAL CENTER PATIENTS
DOGS
FAMILY
HAMSTERS
HAWAIIANS
HUMAN
HUMAN, FEMALES
HUMAN, INFANTS
HUMAN, INFANTS, NEWBORN
HUMAN, MALES
HYDRA
INDIANS, NORTH AMERICAN
INDIANS. SOUTH AMERICAN
INFANT
MAMMALS
MICE
MICROORGANISMS
MOLLUSCA
MONKEYS
NEGROES
PROTOZOA
RABBITS
RATS
RODENTS
TAENIA
VIRUSES

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.

NIDR-CPR-001-(a)-(70)

TITLE OF PROJECT

The efficacy of an adhesive resin in preventing occlusal caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: Herschel S. Horowitz and R. James McCune
Other Investigator: Stanley B. Heifetz
Cooperating Units: Dental Division of the Montana State Health Department

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In May 1970, baseline dental examinations were conducted on 700 grade school children, kindergarten and grades 1, 6 and 7, in Kalispell, Montana, a non-fluoridated community. A total of 450 children were found to have one or more sound pairs of homologous permanent teeth. Only these children were included in the study. One-half the mouth of each subject was randomly designated as the test side and the other half serves as the control. On the test side sound occlusal surfaces were conditioned and sealed with the bisphenol A material developed by Buonocore. Teeth were cleaned in preparation for the sealant by a dental hygienist. However, Public Health Service dentists did the actual conditioning and application. The physical properties of the sealant including the extent of loss will be evaluated periodically during the three-year investigation; follow-up examinations for dental caries increment will be made annually.

Total Man Years: 1 1/4
Professional: 1/2
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
N/A	Herschel S Horowitz	4/12/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.

NIDR-CPR-002-(a)-(68)

TITLE OF PROJECT

The effect of school water fluoridation on dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: Stanley B. Heifetz and Herschel S. Horowitz
Other Investigator: Frank E. Law
Cooperating Units : Dental Health Division, North Carolina State Board of Health, Division of Water Hygiene, Environmental Protection Agency

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In 1968, fluorides were added to the well water supply of a consolidated school (grades 1-12) in Seagrove, North Carolina at 6.3 ppm, seven times the optimal level recommended for community fluoridation in the geographic area. The higher concentration of fluoride is used in an attempt to duplicate the total fluoride intake of children who drink optimally fluoridated water on a full-time basis. Prior to the installation of fluoridation equipment, dental examinations using the DMF tooth and surface index were conducted on approximately 1100 children to determine initial, age-specific rates of caries prevalence. Follow-up examinations will be conducted at four-year intervals to measure the extent of caries protection as increasingly larger segments of the study population become continuously exposed to fluoridated water at school since entering in the first grade. On the eight-year, follow-up examinations an assessment of the prevalence of fluorosis, if any, will be made along with the usual examinations for dental caries.

Total Man Years: 1 1/2
Professional: 3/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
N/A	Stanley B Heifetz	4/12/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: New

NIDR-CPR -003-(a)-(69)

TITLE OF PROJECT

Effects of acidulated phosphate-fluoride chewable tablets on dental caries in school children

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: William S. Driscoll
Other Investigators: Stanley B. Heifetz and Roald J. Shern
Cooperating Units: Dental Health Division, North Carolina State Board of Health and the Public Schools of Wayne County, North Carolina

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forworded to investigators who request such information. Your summary is to be used for these purposes.

Baseline dental examinations were conducted in September 1969 on approximately 1100 first- and second-grade school children in Wayne County, North Carolina. Children assigned to one test group chew an acidulated phosphate-fluoride (APF) tablet containing 1 mg.F, rinse for 30 seconds with the resulting solution and then swallow the material. Another test group follows the same procedure except that they repeat the procedure at least 3 hours later using a second APF tablet also containing 1 mg.F. A third group using a placebo tablet serves as the controls. The treatments are carried out each day in school under supervision of the classroom teacher. Treatments will continue until the participants have completed the eighth grade. Follow-up dental examinations will be conducted at 2-3 year intervals. The first follow-up evaluation (April 1972), and possibly later follow-ups as well, will include an assessment of fluoride uptake by enamel in a sample of the study children using an in vivo biopsy technique.

Total man years: 1 3/4
Professional: 1 1/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
N/A	William S. Driscoll	April 14, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: New

NIDR-CPR -004 (a)-(69)

TITLE OF PROJECT

A study of the effectiveness of two fluoride mouthwashes in controlling dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Stanley B. Heifetz
Other Investigators: William S. Driscoll and William E. Creighton
Cooperating Units: Kaiser Foundation Hospitals, Portland, Oregon and Portland Public Schools

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Baseline dental examinations using the DMF index were conducted in February 1969 on approximately 950 school children in grades 5, 6 and 7, in Portland, Oregon. In addition to the clinical examinations a set of five bite-wing x-rays was taken on each child. The children were separated into three comparable study groups (A, B and C) which carried out the following procedures: Group A rinsed in school once every week with a placebo solution; Group B rinsed weekly in school with a neutral NaF solution containing 0.3 percent fluoride; Group C rinsed weekly in school with an acidulated phosphate-fluoride solution containing 0.3 percent fluoride. Each weekly treatment consisted of two, consecutive, one-minute rinses using 8 ml. of solution. The treatments were carried out in classrooms under supervision of the classroom teachers. The final clinical and radiographic examinations were conducted in February 1971. A paper reporting one- and two-year data is currently in preparation.

Total man years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
N/A	Stanley B. Heifetz	April 14, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-CPR -005-(a)-(69)

Prev. Ser. No.

TITLE OF PROJECT

Evaluation of self-application of stannous fluoride-zirconium silicate prophylaxis paste

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: Herschel S. Horowitz and David Bixler
Other Investigators:
Cooperating Units: Indiana University and Santa Clara County Research Foundation

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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In September 1969, approximately 600 children in grades 5 through 8 were examined independently by two investigators, one from Indiana University and the other from the Public Health Service. Baseline caries scores were determined from both clinical and radiographic assessments. Participants were randomly divided into two groups to brush annually for three years with either a stannous fluoride-zirconium silicate prophylaxis paste (9% SnF_2) or a placebo paste. All treatments are administered under the supervision of a dentist. Follow-up examinations were conducted in September 1970 and 1971. A brief report giving one-year findings has been prepared and submitted to the Santa Clara County Research Foundation. Two-year data are presently being processed. Results of the study should not only be helpful in determining the efficacy, if any, of brushing with the new therapeutic paste but sources of disagreement between examiners in a clinical trial may be pinpointed.

Total man years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
N/A	Herschel S. Horowitz	4-12-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 53

NIDR- CPR -006(b)-71

TITLE OF PROJECT

Preventive-Therapeutic Effects of Actinobolin, An Antimicrobial

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow, CP&RB, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Epidemiology
~~Location: NIDR, NIH, Bethesda, Maryland 20014~~

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Actinobolin, an antimicrobial which appears to have a high specificity for its action against Streptococcus mutans, was originally developed for its use as an anti-tumor agent by Parke-Davis Company. It has been found to be non-effective in the treatment of tumors; however, it appears to have promisein the prevention/control of dental caries. Its mechanism of action is as yet undetermined. It is thought that it blocks protein synthesis in the bacterial cell. It meets all the desired qualifications for an agent that would be desirable for use in the oral cavity in the control of dental caries.

A regimen using "conventional" rats and three concentrations of this agent have been completed. Remaining yet is the scoring of the sectioned jaws of the rats to assess its effectiveness in this trial.

Total Man Years: 1/2
Professional: 1/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. M. Stiles	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -007-(b)-(72)

TITLE OF PROJECT

Plaque Microbiology of Individuals Representing Three Family Generations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow
Other Investigators: None
Cooperating Units: Department of Epidemiology, Johns Hopkins University
School of Hygiene and Public Health

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Caries Prevention and Research
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this effort is to identify high and low risk groups and/or individuals that have remained so over time and to further investigate these individuals for possible responsible factors. The population that has been surveyed for this is a relatively stable one at Hagerstown, Maryland. One parent will be identified as an index case and for whom a DMF record can be retrieved from 20 to 30 years in the past. The spouse and family of this index case will then be sampled for presence and relative numbers of plaque micro-organisms. A test of independence based on a two way classification (DMF and numbers of plaque microorganisms) will be used to assess the two methods of distribution.

Total Man Years: 1/2
Professional: 1/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H M Stiles	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 43

NIDR-CPR-008-(b)-(70)

TITLE OF PROJECT

Relationship of Geographical Location, DMF and Plaque Microorganisms of Venezuelan Yanomamo Indians

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow
Other Investigators: C. J. Donnelly and L. A. Thomson
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Among the Yanomamo Indian Villages of Venezuela are a series of villages located along a river with the establishment of a "Western Mission" at one point in the river, and subsequently a source of "refined" foods that find their way to the villages in various amounts. This study involves the DMF status (as to approximate age) of the individuals in each village, the relationship of plaque microorganisms (particularly Streptococcus mutans) to the DMF and the geographical relationship (distance) of the village to the "Mission."

Total Man Years: 2
Professional: 1 1/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H M Stiles	

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -009-(h)-(72)

TITLE OF PROJECT

Cariogenicity of Plaque Streptococci Isolated from Yanomamo Indians

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow
Other Investigators: Rachel Larson and L. A. Thomson
Cooperating Units: Germfree Unit, Veterinary Resources Branch, NIH

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20016

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The work involves the testing, in animals of known gnotobiosis, various microorganism isolates from the plaques of the Yanomamo Indians of Venezuela. These include Streptococcus mutans (as well as other streptococci) isolates from subjects with high and subjects with low caries incidence. By comparing the "caries-producing-potential" of these organisms in both gnotobiotic and "conventional" animals (in this case rats) insight may be gained into the mechanism of such production by any or all of these designs.

Total Man Years: 1/4
Professional: 1/4
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. M. Stiles	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -010-(b)-72

TITLE OF PROJECT

In-Vivo Effect of Fluoride on Oral Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow
Other Investigators: R. A. Frew, Senior Dental Surgeon
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This is limited information available on the in-vitro effect of the fluoride ion on oral microorganisms and even less on the in-vivo effect, if any.

Proposed work involves approaching this question using animals, both infected and non-infected with a caries-inducing streptococcus with a fluoride regimen given both pre- and post-infection. The plaque produced in these animals will be monitored periodically for numbers and kinds of microorganisms.

Total Man Years: 1/2
Professional: 1/2
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. M. Stiles	

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -011-(b)-72

TITLE OF PROJECT

Clarification of the Hamster Model System for Evaluation of Microorganism Cariogenicity

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. M. Stiles, Senior Staff Fellow
Other Investigators: R. A. Frew, Senior Dental Surgeon
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Caries Prevention and Research Branch
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Recently the hamster caries model system has not been effective. This was thought to possibly have been caused by one or a combination of factors:

1. change of source of hamsters;
2. loss of virulence (via culture passage, etc.) of the infecting organism;
3. animal immunity.

Consequently, it was planned to investigate each of these factors as a possible cause of failure.

This work has been completed utilizing hamsters from the NIH Animal Production Unit (source of the hamsters used in first developing the model caries testing system) and hamsters from a contracting source outside of NIH. Three different isolates of 6715 (Streptococcus mutans) were tested for their cariogenicity.

Total Man Years: 1/2
Professional: 1/2
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H M Stiles	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR- CPR -012 (b) -72

TITLE OF PROJECT

Streptococci Present in Human Dental Plaque

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: L. Ariel Thomson, DDS, Dr. Ph.

H. M. Stiles, DDS, Ph.D.

Cooperating Unit: Center for Disease Control, Atlanta, Georgia

Dr. Richard Facklam

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institutes of Health, PHS, National Institute for Dental Research, Epidemiology Section, Caries Prevention and Research Branch, Westwood Bldg. Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Description: An atlas including descriptive material, identification criteria, biochemical characteristics, serological reactions and photographic plates will be assembled on streptococci normally present in dental plaque. The photographs will include both color and black and white plates showing typical and atypical colony morphology on Mitis-Salivarius agar from the normal superior position, as well as in profile. Information on current species identification will be provided as available from members of the International Subcommittee on Streptococci and Pneumococci Streptococci described in the atlas will include dental plaque strains from many different geographical regions and reference strains from the National Center for Disease Control, American Type Culture Collection and prominent plaque investigators.

It is anticipated that an Atlas on plaque streptococci could aid new workers in this fast growing field and encourage discussions, cooperation and lead hopefully to an eventual consensus among plaque workers.

Total Man Years: 3/4
Professional : 1/2
Other : 1/4

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L. Ariel Thomson	

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -013-(b)-72

TITLE OF PROJECT

Application of Fluorescent Antibody (FA) Techniques in Dental Plaque Studies

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Coinvestigators: L. Ariel Thomson, DDS, Dr. PH
George Hageage, Ph.D.

Other investigators: H. M. Stiles, DDS, Ph.D.

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institutes of Health, National Institute of Dental Research, Caries Prevention and Research Branch, Westwood Bldg., Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Animal studies have implicated certain dental plaque streptococci and actinomycetes as etiologic agents in periodontal disease and dental caries. Epidemiologic studies are indicated but have been limited by the inability to rapidly detect and quantify specific strains. New developments in FA capabilities and equipment appear to permit such studies.

Reagent grade FA conjugates specific for certain actinomyceetes have been prepared by Georg (J. Bact. 97, 581-88, 1969). Bratthal has reported (IADR Abstracts, p. 66, 1972) the preparation of S. mutans conjugates. The availability of these and other conjugates improved to reagent grade will permit the use of the new quantitation methods.

Preliminary studies indicate that direct FA staining of colonies adhering to agar plates gives an estimate of the ratio of specific stained bacteria to those cultivable in plaque specimens (Hageage, IADR Abstracts, p. 241, 1972). FA stained smears or colonies on membrane filters provide alternate quantitation methods. These diagnostic methods require reagent grade conjugates and the new incidence light FA excitation. Further investigations are underway to evaluate these FA quantitation methods and determine their application in epidemiologic studies.

Total Man Years: 3/4
Professional: 3/4
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L. Ariel Thomson	

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 46

NIDR- CPR -014-(b)-71

TITLE OF PROJECT

A New Transport Medium for the Preservation of Oral Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: B. Rundell
Other Investigators: L. A. Thomson and H. M. Stiles
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention and Research
Section: Epidemiology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Various transport media for different types of bacterial specimens have been reported in the literature by Stuart, Möller and Gästrin. These media were developed principally for pathogens and whose storage temperatures affected viability of the bacterial cells. These studies did not include an evaluation of the survival of common oral bacteria.

Recent Loesche created a new medium for the transportation and dispersion of plaque specimens. Its formation contains agents to enhance cell dispersion, eliminate possible toxic effects of trace heavy metal ions, and to maintain a lower and more stable Eh than older transport media. Observations were limited to Streptococci (in the present study) due to the relative ease in differentiating species on Mitis-Salivarius agar, and the recent interest in the role of Streptococci in the formation of caries. Large studies involving field studies necessitate a thorough examination of desirable transport-holding media.

Total Man Years: 3/4
Professional: 3/4
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Barbara Rundell	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- CPR -015(b)(70)

Prev. Ser. No. 51

TITLE OF PROJECT

Cross Validation of Zoogleic Index

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal: Dr. Roald Shern

Other: Dr. Charles J. Donnelly

NAME AND ADDRESS OF APPLICANT INSTITUTION National Institutes of Health, National Institute of Dental Research, Westwood Bldg. Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study was to ascertain what bacteria contributed to the association of the index with dental caries. A second objective was to use the mixed flora aggregation as a response variable to screen various antiseptics. From the index wire samples were taken and the microcosm was speciated. In the second phase, the bacterial mass of each individual was challenged with alexidine, amine fluorides, chlorhexidine, and cetyl pyridinium chloride.

Many bacteria contributed to the growth on the wires.

These bacteria included:

L. Acidophilus var. casei, S. Faecalis, S. mutans, S. Sanguis, S. Salivarius, and some non-speciated filaments. All of these organisms have been implicated in the carious process.

An initial attempt to use the index as a response variable antiseptics was conducted.

Total Man Years 1/2
Professional 1/2
Other

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J Shern	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. New

NIDR- CPR -016(b)(72)

TITLE OF PROJECT

Development of Analytic Methods for Various Antiseptics

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal investigator:: Dr. Roald Shern

Other investigator: Miss Barbara Rundell

NAME AND ADDRESS OF APPLICANT INSTITUTION National Institutes of Health, National Institute of Dental Research, Caries Prevention and Research Branch, Westwood Bldg., Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Several antiseptics, which have been shown able to suppress plaque calculus and gingivitis, have no reported analytic technique. Methods of assay are needed for safety studies and mechanism studies including an ongoing screening study.

Analytic methods for alexidine, hibitane, amine halides and certain quaternary ammonium compounds are being developed.

Methods were developed for quantification of antiseptics. An anionic-cationic titration method was developed for the amine fluorides.

A spectrophotometric method was developed for some quaternary ammonium compounds as well as for some amine fluorides.

So far no satisfactory method has been reported for the biguanides, thus a method for their quantitation will be sought.

Total Man Years 1/2
Professional 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald Shern	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 52

NIDR- CPR -017-(b)-71

TITLE OF PROJECT

Adsorption of Cationic Antiseptics on Tooth Enamel

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal investigator: Dr. Roald Shern

Other investigator: Miss Barbara Rundell

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institutes of Health, National Institute of Dental Research, Caries Prevention and Research Branch, Westwood Bldg., Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Currently cationic antiseptics are being screened for their ability to restrict bacterial aggregation on enamel, to quantify the adsorbed antiseptic and to screen these adsorbed films for their ability to restrict enamel dissolution. Minimal glycolytic and growth concentrations are also being assessed. Various (GRAS) approved antimicrobials will be assessed.

Total Man Years 1
Professional 3/4
Other 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J Shern	

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 57

NIDR- CPR -018-(b)-(70)

TITLE OF PROJECT

A Survey of the Teeth and Supporting Bone of a Sample of Skulls from the Terry Collection

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Charles J. Donnelly, DDS
Caries Prevention & Research Branch, NIDR
Other: Robert Fogarty, G. Carter, P. Taghe and Miss Brunelle
Cooperating Units: Dept. of Physical Anthropology
Smithsonian Institution

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institutes of Health, National Institute of Dental Research, Caries Prevention and Research Branch

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Approximately 1,000 skulls (2/3 random sample) from the Terry collection were selected and measurements were made on the 753 with teeth. Evidence of caries experience in coronal and radicular tooth surfaces was recorded. Bone level was measured with a graduated periodontal probe and recorded to the nearest millimeter for mesial, distal, lingual and labial surfaces of all teeth present using the cemento-enamel junction as the reference point. Direct observations were made of infrabony pockets, fenestration, dehiscence and other defects. The data has been processed and is presently being analyzed.

Total Man Years: 2
Professional: 1 1/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Charles J. Donnelly	

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-48 (59)

NIDR- CPR -019-(b)-72

TITLE OF PROJECT

Pathogenic Bacterial Mats on Human Teeth. 1. Diagnosis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. P. H. Keyes, Chief, Laboratory Studies Section, CPRB, NIDR
Other Investigators: Dr. G. J. Hageage, Res. Micro., Lab. of Biological Structure, NIDR
Cooperating Units: Dr. H. V. Jordan, Forsyth Dental Center, Boston, Mass.
Dr. R. G. Schamschula, Institute Dental Research, Sidney, Australia
Mr. S. Bellack, Lincoln State School, Lincoln, Ill.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention & Research Branch
Section: Laboratory Studies Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Adherent coats of germ life on the crowns and roots of teeth, when conditions are favorable, cause odontolysis of the teeth (dental caries) and inflammatory lesions in their supporting tissues (periodontitis). For example, on enamel surfaces highly acidogenic mats with a streptococcal component may cause coronal cavitation. Apparently, less acidogenic mats that have an actinomycotic component to that form on the cervical and radicular surfaces may lead to periodontal recession, root caries, alveoloclasia, and the autogenous exfoliation of the teeth. Work continues to develop better methods for the identification of streptococci and actinomyces known to have an odontopathic potential. Special attention has been placed on the characteristics of micro-colonies of these organisms, and work with fluorescent antibody technics is anticipated.

Total Man Years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	P. H. Keyes	5.12.72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-48 (59)

NIDR- CPR -020-(b)-(59)

TITLE OF PROJECT

Pathogenic Bacterial Mats on Human Teeth. 2. Treatment Measures

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. P. H. Keyes, Chief, Laboratory Studies Section, CPRB, NIDR
Other Investigators: Dr. G. J. Hageage, Res. Microbio., Lab of Biological Structure, NIDR
Cooperating Units: Dr. H. V. Jordan, Forsyth Dental Center, Boston, Mass.
Dr. R. G. Schamschula, Institute Dental Research, Sidney, Australia
Mr. S. Bellack, Lincoln State School, Lincoln, Ill.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention & Research Branch
Section: Laboratory Studies Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Highly invasive and destructive coats of germ life on teeth cannot always be reduced to innocuous levels with tooth brushes, flosses, and other mechanical devices. Chemotherapeutic measures have been considered for many years, but unfortunately little progress in acceptance has been attained. Nevertheless, the need persists, and our attention is still being given to assays of antibacterial agents in in vitro models. Adherent coats of S. mutans or A. viscosus grown on the surfaces of wires or teeth are exposed to antibacterial agents, enzymes, and other compounds in order to determine if the exposure will kill or retard growth of the above mentioned pathogens.

Total Man Years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	P H Keyes	5-12-72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.
Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-48 (59)

NIDR- CPR -021-(b)-(59)

TITLE OF PROJECT

Pathogenic Bacterial Mats on Human Teeth. 3. Etiological factors

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. P. H. Keyes, Chief, Laboratory Studies Section, CPRB, NIDR
Other Investigators: Dr. G. J. Hageage, Res. Micro., Lab. of Biological Structure, NIDR
Cooperating Units: Dr. H. V. Jordan, Forsyth Dental Center, Boston, Mass.
Dr. R. G. Schamschula, Institute Dental Research, Sidney, Australia
Mr. S. Bellack, Lincoln State School, Lincoln, Ill.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention & Research Branch
Section: Laboratory Studies Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Lines of communication have been kept open with Dr. Harold V. Jordan, Forsyth Dental Center, Boston, Mass. and Mr. Stephen Bellack, Lincoln State School, Lincoln, Illinois, in order to investigate microorganisms isolated from bacterial mats on human teeth. An actinomycete-like organism isolated from a retarded child has induced highly destructive lesions in the roots and periodontal tissues of mono-infected rats. An isolate of Neisseria sicca was not pathogenic under similar conditions. The studies in germ free animals were done in Boston.

Total Man Years: 3/4
Professional: 3/4
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	P H Keyes	5-12-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-54 (70)

NIDR- CPR -022-(h)-(70)

TITLE OF PROJECT

A Study of the Mode of Action of Fluoride Treatment in Experimental Dental Caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. R. H. Larson, Research Chemist
Other Investigators: None
Cooperating Units: The Kendall Company, Barrington, Illinois

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Caries Prevention & Research Branch
Section: Laboratory Studies Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A series of rat studies is being run in an effort to gain more information as to the mode of action of fluoride in the reduction of caries. Fluoride is being administered at various concentration in the diet, in the drinking or by stomach tube, for both long and short intervals and to animals of different ages. As a result of these studies it will be possible to study the interrelationship between intake, uptake, the influence on oral microflora and the development caries.

Total Man Years: 3 1/4
Professional: 1
Other: 2 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard N. Larson	4-21-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.-NONE

NIDR-CPR -023-(c)-72

TITLE OF PROJECT

Assessment of Occlusal Status

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Terrence J. Freer
Other Investigators : NONE

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Caries Prevention & Research Branch
Section : Biometry Section
Location : NCP, NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A variety of indices of malocclusion has been proposed for the quantitative or numerical assessment of the occlusal status of an individual. The basis of these indices has been the clincian's interpretation of overall severity.

The numerical diagnosis of any clinical condition assumes that the deductive processes of the clinician can be satisfactorily approximated by some mathematical model. Errors in the quantitative estimation of the severity of malocclusion may arise from at least three sources:

1. errors of measurement of descriptive attributes
2. errors of approximation in the mathematical model
3. errors of accuracy and consistency in the clinician's severity estimates

Attention will be directed to investigation of the various numerical methods which might be used to express the relationship between the clinician's severity assessment of an individual's occlusion and the various descriptive occlusal attributes which may be measured on that individual.

The methods of numerical taxonomy, which are free of assumptions concerning the underlying distributions of the data, offer an intuitively more appealing approach to classification and prediction than multivariate linear models. For this reason priority will be given to further investigation of numerical taxonomic methods in the assessment of occlusal status.

Total Man Years: 3/4
Professional: 1/2
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. E. Freer Dr. Terrence J. Freer, NCP, CP&RB, NIDR	4-25-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.-NONE

NIDR-CPR -024-(c)-(72)

TITLE OF PROJECT

Agreement Among the Subjective Severity Assessments of Orthodontists

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Terrence J. Freer
Other Investigators : John M. Grewe, D.D.S., Ph.D.
Robert M. Little, D.D.S., M.S.D.
Cooperating Units : Dental School, University of Maryland, Baltimore

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Caries Prevention & Research Branch
Section : Biometry Section
Location : NCP, NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Quantitative methods for assessing the severity of malocclusion assume that there is a reasonably consistent relationship between an orthodontist's subjective severity assessment and the measured attributes of an individual's occlusion. If this assumption is untrue, numerical methods will be unsuccessful. There is sufficient evidence available to justify this assumption.

However, given the importance of the levels of agreement among the subjective assessments of orthodontists, this subject has received surprisingly little attention. Previous research indicates that the actual severity status of the occlusion being assessed influences inter-examiner variation. The less severe the malocclusion, the greater is the variation.

Research was primarily directed to investigation of the levels of agreement among the clinical severity scores of 10 orthodontists who assessed the same 98 sets of study models. Because of the importance of subjective severity assessments in the development of quantitative assessment methods, such data would be a valuable contribution to the overall research of quantitative assessment methods.

Total Man Years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Terrence J. Freer, NCP, NIDR, NIH	4-25-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Serial No. New

NIDR-CPR -025-(b)-72

TITLE OF PROJECT

Root surface caries: Prevalence in a Human Population

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Harold R. Englander, Chief, Field Trials, CP&RB, NIDR
Other Investigators: Harold V. Jordan, Forsyth Dental Center
David L. Sumney, Harvard School of Dental Medicine
Cooperating Units: Forsyth Dental Center, Boston, Mass.

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institute of Dental Research, NIH, Bethesda, Maryland

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

To assess the prevalence of root surface caries on individuals on Governors Island, NY and other government and civilian clinics in NYC.

For purposes of this study, cemental caries is defined as erosive lesions in tooth structure below the cemento-enamel junction and are characterized by softening, discoloration and usually cavitation in the affected area. This definition excludes abrasive lesions of the cementum which have a different etiology and clinical appearance. Nonrestorable lesions are also enumerated. Panorex radiographs are used.

The distribution of the proposed population is as follows:

Age in years	No. of subjects* Male	Female
30 - 40	100	100
40 - 50	100	100
50 - 60	100	100
All ages	300	300

*All persons must have at least 20 natural teeth.

Total Man Years: 1 3/4
Professional: 1 1/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Serial No. 42

NIDR- CPR -026(b)-69

TITLE OF PROJECT

Epidemiologic Studies on the Implantation and Transmissibility of Caries-conducive Streptococcal Strains and Relation between S. mutans and Smooth Surface Caries in the Deciduous Dentition (NIDR-01)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. R. Englander, Chief, Field Trials, CP&RB, NIDR
Other Investigators: H. V. Jordan, D.D.S. and H. E. Stiles, DDS
Cooperating Units: Forsyth Dental Center and Governors Island, NY

NAME AND ADDRESS OF APPLICANT INSTITUTION

National Institute of Dental Research, Bethesda, Maryland

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A potentially caries-inducing streptococcal strain (S. mutans, S. sanguis or others) is isolated from at least one parent made resistant to streptomycin, and reimplanted in the oral cavity of the donor parent. To study implantation and persistence of the organism, plaque samples are cultured periodically on Mitis salivarius agar. Conditions favoring implantation will be investigated and it is intended to study all possible lines of transmission of the implanted strains within families.

To survey the presence of S. mutans in plaque and dental caries experience on smooth surfaces of the deciduous teeth in a group of 93 Caucasian, pre-school children, aged 19-54 months on Governors Island, NY. To detect children harboring S. mutans plaque samples were collected from all tooth surfaces of each child with a cleoid carver, cultured on Mitis salivarius agar, and isolates identified.

Total Man Years: 1 3/4
Professional: 1
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-1

NIDR- DIR -001-(a)-(68)

TITLE OF PROJECT

Laboratory Automation System

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Mr. John J. Wilson, Chief, Computer Processing and Analysis Section
Other Investigators: Mr. Frederick J. Brown, Electronic Engineer
Cooperating Units: Computer Systems Laboratory, Division of Computer Research and Technology, NIH

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Computer Processing and Analysis Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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This project is a joint collaborative endeavor on the part of NIDR and of the Division of Computer Research and Technology, NIH.

It is a laboratory automation project which is involved in the concurrent on-line acquisition and real time processing of data from a number of analytical instruments and experiments. The project also involves the control of bacteria growth experiments. The computer complex (Honeywell H-316 and H-516) operates under the OLERT multiprogramming operating system. The system is interfaced with an amino acid analyzer, liquid scintillation counters, a spectrophotometer, a gas chromatograph and neurophysiology microelectrode experiments. Telecommunication with the NIH central IBM 370 computer facility is being established.

Total Man Years: 4 1/4
Professional: 1 1/4
Other: 3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John J. Wilson	4/25/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-DIR -002-(a)-(72)

TITLE OF PROJECT

Laboratory Automation Software

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Mr. William I. Wood, Assistant Health Services Officer
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Computer Processing and Analysis Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

1. Multiprogramming Systems Software for the NIDR Laboratory Automation System: Modification and improvement of the OLERT real-time operating system to encompass two processors, a Honeywell DDP-516 and H-316, using dynamic disc switching.

2. Data Acquisitions Software: Real-time programs for the acquisition of amino acid analyzer data via an analog to digital converter and for the acquisition of neurophysiology pulse data.

3. Processing of Chromatography Data: A series of programs for the integration and identification of amino acid analyzer, gas chromatograph, and disc gel electrophoresis data. This processing is done on the IBM 360/370 computers at the Division of Computer Research and Technology, NIH

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William I. Wood	4/25/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-11

NIDR-DIR -003-(b)-(70)

TITLE OF PROJECT

The Activity of Trigeminal Afferent Fibers of the Monkey in Response to Painful and Thermal Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: Dr. Rhyuji Sumino, Visiting Scientist
Dr. Ronald Dubner, Chief, Neural Mechanisms Section
Other Investigators: Dr. Robert H. Friedman, Research Associate
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Under barbiturate anesthesia, thin nerve bundles are dissected from the infraorbital and inferior alveolar nerves, and their electrical activity recorded and stored on magnetic tape. Thermal and noxious heat stimuli are delivered with a precisely-controlled thermode which has a temperature range of 20°C to 60°C and can produce a temperature change of 10°C at the thermode-skin junction within one second. Data is analyzed with the aid of an on-line, real-time computer system.

Total Man Years: 2 1/2
Professional: 1 3/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	R. Sumino	4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-DIR -004-(a)-(71)

TITLE OF PROJECT

A Computer Program for the Analysis of Trigeminal System Single Unit Discharges in Response to Oro-facial Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Robert H. Friedman, Research Associate
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The response properties of trigeminal afferent fibers and brain-stem neurons to controlled sensory stimuli are studied with the aid of an on-line, real-time computer system. Appropriate software is being developed to input, store, retrieve, and process data and display the processed data graphically in the laboratory.

Total Man Years: 3/4
Professional: 3/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert H. Friedman	4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- DIR -005-(b)-(65)

Prev. Ser. No. NIDR-12

TITLE OF PROJECT

The Response Properties of Neurons in the Trigeminal Brain-stem Nuclear Complex of the Monkey

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigators: Dr. Ronald Dubner, Chief, Neural Mechanisms Section
Dr. William D. Thompson, Senior Veterinarian Officer

Other Investigators: None

Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Microelectrode recordings from the rostral and caudal divisions of the trigeminal brain-stem nuclei are performed in awake, restrained monkeys. Mechanical and thermal stimuli are applied to the face and oral mucosa and the response properties of single neurons are recorded and stored on magnetic tape. Data is analyzed with the aid of an on-line, real-time computer system.

Total Man Years: 2 3/4
Professional: 1
Other: 1 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Ronald Dubner	4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-10

NIDR- DIR -006-(b)-(66)

TITLE OF PROJECT

Anatomical Studies of the Organization of the Main Sensory and Spinal V Nuclei

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Stephen Gobel, Senior Dental Surgeon
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project involves light and electron microscopical studies of the neuronal morphology and organization of the neuropil of the main sensory and spinal V nuclei in rats, cats and monkeys. The objectives of these studies are to broaden our understanding of orofacial sensation and the mechanisms of pain.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stephen Gobel	4/19/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-DIR -007-(a)-(69)

Prev. Ser. No. None

TITLE OF PROJECT

Neurophysiologic Instrumentation, Laboratory Instrumentation and Computer Interfacing of Laboratory Instrumentation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Mr. Frederick J. Brown, Electronic Engineer
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This work involves the development of suitable electronic and electromechanical instrumentation to be used in neuro-physiological research. It involves the adaptation and interfacing of these and other instruments to a multipurpose computer installation.

Total Man Years: 1/2
Professional: 1/2
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Frederick J. Brown	4/25/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-2

NIDR- DIR -008-(b)-(68)

TITLE OF PROJECT

Control of Aggregation and Differentiation by Cyclic-AMP in Dictyostelium Discoideum

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Bruce M. Chassy, Research Chemist
Other Investigators: Mr. Leslie L. Love, Biological Laboratory Technician
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Prepared purified antibody toward cyclic nucleotide phosphodiesterase and used same to demonstrate that the enzyme is an obligate part of the aggregative system in D. discoideum.

Demonstrated that at least two of the multiple forms of the enzyme could be interconverted and suggested a functional developmental role for the existence of 2 catalytic forms.

Initiated the chemical synthesis of some cAMP analogs.

Attempted the identification of adenyl cyclase activity in the slime mold.

Total Man Years: 1 3/4
Professional: 1/2
Other: 1 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Bruce M. Chassy	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- **DIR** -009-(b)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Time Lapse Photographic Studies of Aggregation and Differentiation in Dictyostelium Discoideum

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Mr. Leslie L. Love, Biological Laboratory Technician
Other Investigators: Dr. Micah I. Krichevsky, Chief, Environmental Mechanisms Section
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In order to correlate the biochemical changes during differentiation with the visually apparent morphogenetic changes, we are using time lapse cinematography of the process under different environmental conditions. Thus, we can measure the rate of propagation of the wave motion in the aggregating stage as well as the psuedoplasmodium.

In the initial stages of aggregation it is possible to observe the development of heterogeneous cell populations and to correlate the movement of the cells with modifying conditions such as the presence of cyclic AMP.

Total Man Years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Leslie L. Love	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-1

NIDR- DIR -010-(b)-(60)

TITLE OF PROJECT

Metabolism of 5'-Mononucleotides in Dictyostelium Discoideum

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Micah I. Krichevsky, Chief, Environmental Mechanisms Section
Other Investigators: Mr. Leslie L. Love, Biological Laboratory Technician
Dr. Bruce M. Chassy, Research Chemist
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Since mononucleotides specifically accelerate the rate of early differentiation, we are studying their metabolism. By use of isotopically labelled mononucleotides, it appears that the pathways are relatively simple. On chromatography, few metabolites appear to be generated from the original substrates. However, some of these spots are unknown at this time and are the subject of current investigation.

Total Man Years: 1 1/4
Professional: 3/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Micah I. Krichevsky	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- DIR -011-(a)-(70)

Prev. Ser. No. NIDR-6

TITLE OF PROJECT

Growth Rate of Dextran-Forming Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Jacob A. Donkersloot, Staff Fellow
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In order to develop a mathematical expression for growth of cariogenic streptococci on sucrose, a more sensitive method for DNA as a measure of cell numbers is required. A fluorometric assay method using ethidium bromide was developed. The method is applicable to measurement of bacterial cellular DNA in pure cultures, even in the presence of dextran, as well as in human dental plaque.

Total Man Years: 1
Professional: 3/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jacob A. Donkersloot	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-DIR -012-(a)-(71)

Prev. Ser. No. None

TITLE OF PROJECT

On-line Computer Control of Microbial Fermentations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Jacob A. Donkersloot, Staff Fellow
Other Investigators: Mr. Frederick J. Brown, Electronic Engineer
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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A pH monitoring system, suitable for use with an on-line computer, was developed. It is insensitive to grounding problems. As many as three specific ion electrodes can be used at the same time in the system, thus allowing multiparametric continuous monitoring of the events in the fermentation.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Jacob A. Donkersloot

DATE: 5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR- DIR -013-(b)-(71)

TITLE OF PROJECT

Extracellular Polysaccharide Formation by Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Stanley A. Robrish, Research Microbiologist
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Using glucosyl and fructosyl specifically labeled sucroses to calculate the ratios of glucan and fructan in the polysaccharide formed from different strains of S. mutans. The extracellular polysaccharide is able to bind the enzyme or enzymes responsible for its own synthesis.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley A Robrish	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR- DIR -014-(b)-(71)

TITLE OF PROJECT

Sucrose Metabolism by Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Bruce M. Chassy, Research Chemist
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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In order to study the various enzymatic systems responsible for the primary attack on the sucrose molecule by cariogenic streptococci, we are beginning the chromatographic purification of polysaccharide producing enzymes. The invertase activities are also being isolated for characterization. New techniques for making specifically labelled sucroses have been developed.

Total Man Years: 1/2
Professional: 1/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Bruce M Chassy	5/3/72

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METHOD OF SUPPORT *(Check one)*

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- DIR -015-(a)-(71)

Prev. Ser. No. None

TITLE OF PROJECT

On-line Computer Measurement of Turbidity in Microbial Cultures

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Micah I. Krichevsky, Chief, Environmental Mechanisms Section
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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A prototype autoclavable probe has been built. It uses a light emitting diode at 630 nm as a source of monochromatic light. The light is transmitted in and out of the culture by image conduit. A PIN photodiode is used as the light sensor. A special dual amplifier circuit is used to match the output range of the photodiode to the input of the computer to maximize the sensitivity throughout the normal bacterial growth range.

Total Man Years: 1 1/4
Professional: 1/4
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Micah I. Krichevsky	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR- DIR -016-(a)-(71)

TITLE OF PROJECT

Handling of Microbial Strain Information by Computers

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Micah I. Krichevsky, Chief, Environmental Mechanisms Section

Other Investigators: Mr. Morrison Rogsa, Research Microbiologist, Microbial Physiology Section, Laboratory of Microbiology, NIDR

Cooperating Units: Dr. L. Norton, Heuristics Laboratory, Division of Computer Research and Technology
Dr. R.R. Colwell, Biology Department, Georgetown University
American Type Culture Collection
Professor V. Skerman, Univ. of Queensland, Brisbane, Australia

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Definition and standardization of the questions that are asked about microbial strains in a computer-compatible form is the first goal. Programs are being developed to enter data and retrieve it in a variety of ways for epidemiological, diagnostic, taxanomic, ecological, etc. uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Micah I Krichevsky	5/3/72

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METHOD OF SUPPORT *(Check one)*

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR- DIR -017-(a)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Use of an On-line Computer as a Laboratory Instrument

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Bruce M. Chassy, Research Chemist
Other Investigators: None
Cooperating Units: Mr. L. Freeman, Division of Computer Research and Technology

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Section: Environmental Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Under the operating system of the NIDR computer, proceedures were developed to acquire data from the gas chromatograph and calculate areas under the curves.

The Gilford spectrophotometer was interfaced with the same computer. A complex set of modular programs is in various stages of development for the multiplicity of uses possible with this instrument, including enzyme kinetics, end point assays, scanning densitometry, spectral analysis, etc.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Bruce M. Chassy	5/3/72

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-DS -001-(c)-(72)

TITLE OF PROJECT

Dental Care for the Clinical Center Patient Population

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Samuel Kakehashi, Chief, Dental Services Branch, NIDR
Co-Investigators: Dr. John Folio, Dental Services Branch, NIDR
Dr. Patrick Looney, Dental Services Branch, NIDR
Dr. Paul Lund, " " " "
Dr. Warren Baer, " " " "
Dr. William Beck, " " " "
Dr. Stephen Fred, " " " "
Dr. Robert Leigh, " " " "

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Consultations and necessary dental care are extended to the research patient population of the Clinical Center. Services are limited to dental treatment germane to the medical care and research requirements of patients undergoing active study in one of the intramural clinical research programs at the National Institutes of Health.

Total Man Years: 6 1/4
Professional: 6 1/4
Other 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		4/21/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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Not for publication or publication reference.

NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 102

NIDR-DS -002-(c)-(68)

TITLE OF PROJECT

A Study of Differences in Occurrence of Dental Caries in Caucasian and Negro Children

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Samuel Kakehashi, Chief, Dental Services Branch, NIDR
Co-Investigator: Dr. Norman W. Littleton, Richmond, Virginia
Other Investigators: None
Cooperating Units: Forsythe Dental Clinic, Boston, Massachusetts

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies to determine the dental caries experience and clinical evidence of fluorosis in samples of Caucasian and Negro children have been undertaken. An analysis of enamel biopsy data is currently in progress.

Total Man Years: 1/8
Professional: 1/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		4/21/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 101

NIDR-DS -003-(c)-(66)

TITLE OF PROJECT

A Long-term Study of Periodontal Disease in a Stable, Adult, Male Population

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Samuel Kakehashi, Chief, Dental Services Branch, NIDR
Co-Investigators: Dr. Norman W. Littleton, Richmond, Virginia
Cooperating Units: District of Columbia Fire Department

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The relationship between the various clinical signs of periodontal diseases has not been adequately described. Limitations associated with the clinical and cross-sectional epidemiological study of periodontal diseases, a chronic and progressive process, are well recognized. Consequently, the need for a long-term study is not only indicated but appears to be the only method by which this information can be obtained.

An initial periodontal examination of 581 male volunteers has been completed. The second series of field examinations have been delayed. In the interim, statistical analysis of the data obtained from the first examination will continue.

Total Man Years: 1/8
Professional: 1/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		Feb 1 72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 103

NIDR-DS -004-(c)-(67)

TITLE OF PROJECT

Tissue Healing Following Oral Surgical Procedures

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Patrick Looney, Dental Services Branch, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A study to delineate the relationship of localized osteitis following oral surgical extractions to local, systemic, constitutional and operative factors.

Pertinent pre and postoperative data are recorded and patients are kept under close observation until surgical sites are asymptomatic postoperatively.

Total Man Years: 1 5/8
Professional: 1/8
Other: 1 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Patrick D. Looney	5/1/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 104

NIDR-DS -005-(c)-(67)

TITLE OF PROJECT

Roentgenographic Study of the Temporomandibular Joint Following Osteotomy of the Mandibular Rami

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Patrick Looney, Dental Services Branch, NIDR
Co-Investigator: Dr. John Folio, Dental Services Branch, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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There continues to be many unanswered questions as to what happens to the temporomandibular joints following bilateral osteotomy of the mandible. To date, only sparse long-term postoperative data are available.

This study utilizes several different surgical techniques and the patients are followed for as long as possible. X-ray and clinical examinations are undertaken each year to evaluate changes in the occlusion or temporomandibular joint symptoms.

Total Man Years: 3/8
Professional: 3/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Patrick D. Looney	5/1/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-DS- 006-(a)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

A Determination of the Presence and Location of Gamma 2 Phase in Dental Amalgams as Related to Tarnish and Corrosion

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Stephen R. Fred, Dental Services Branch, NIDR
Co-Investigator: Dr. Richard Waterstrat, A.D.A. Research Associate, NBS, Gaithersburg, Md.
Other Investigators: Dr. Edward D. Eanes, Chief, Molecular Structure Section, LBS, NIDR
Dr. David Greenfield, Molecular Structure Section, LBS, NIDR
Cooperating Units: National Bureau of Standards, Gaithersburg, Md.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Dental Services Branch
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK — *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

An attempt is being made to identify the gamma 2 phase (mercury-tin) and its geography in amalgams. This phase, thought to be responsible for amalgam tarnish and corrosion may be found concentrated in certain areas of the final amalgam filling. Six amalgam alloys are being studied, two of which are reported to have little or no gamma 2 phase in the final amalgam.

Electron microprobe and x-ray diffraction studies of these amalgam surfaces may lead to new ideas of the nature of gamma 2 phase location and its role in tarnish and corrosion.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stephen R. Fred DDS	5/1/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-81 (64)

NIDR-EPB -001-(b) (64)

TITLE OF PROJECT

Histochemical and chemical studies of normal and diseased tissues

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. W. A. Gibson
Other Investigators: None
Cooperating Units: Dr. H. Schwartz, Dr. R. Delfini
Dept. Periodontology, Georgetown Univ., Washington, D.C.
Dr. G. Bowers, U.S. Navy Dental School, Bethesda, Md.
Dr. H. Spencer, Hines V.A. Hospital, Hines, Ill.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Experimental Pathology Branch
Section: Histochemistry Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Histochemical and chemical studies carried out in normal and diseased tissues to determine the basic mechanisms involved in the pathogenesis of various oral diseases. Emphasis is placed on qualitative and quantitative changes in the various enzyme activities reflecting changes in basic metabolic activities. Periodontal tissues in folic acid deficiency states, enzyme histochemistry and fluorescent antibody localizations of various immunoglobulins in human dental plaque are currently being investigated.

Total Man Years: 5
Professional: 1
Other: 4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William A. Gibson	2 May 72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-84 (66)

NIDR-EPB -002-(b) (66)

TITLE OF PROJECT

Histochemical and biochemical studies of connective tissues

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: J. F. Goggins
Other Investigators: L. G. Raisz, A. R. Severson
Cooperating Units: G. S. Johnson and I. Pastan, NCI

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Experimental Pathology Branch
Section: Histochemistry Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this study is to examine the biosynthesis and degradation of connective tissue acid mucopolysaccharides in the normal and diseased states. In vitro methods are used to examine these processes and the factors that affect them.

Total Man Years: 4
Professional: 1
Other: 3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John F. Goggins	5/2/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-82(63)

NIDR-EPB-003-(a)-63

TITLE OF PROJECT

Clinico-pathologic Studies of Human Oral Mucosa

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Howell O. Archard, DDS, Chief, Diagnostic Pathology
Other Investigators: None
Cooperating Units: National Cancer Institute, Laboratory of Pathology
National Cancer Institute, Dermatology Branch

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Experimental Pathology
Section: Diagnostic Pathology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Human oral mucosal lesions of a keratotic nature are studied clinically and histologically over their duration for changes occurring in them. Lesions studied include hyperplastic, pre-malignant, and inherited mucosal disorders. Each case undergoes a detailed environmental analysis, appropriate laboratory studies are performed, and a record of the clinical and histologic changes is obtained in order to document the clinicopathologic progression of the disease.

Where indicated, appropriate correlative studies, such as histochemistry, electron microscopy, biodynamic (turnover) studies, immunofluorescent procedures, etc., are employed to provide additional significant data.

Total Man Years: 1½
Professional: ½
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: H. O. Archard DDS

DATE: 4/21/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-83(66)

NIDR-EPB -004-(a)-66

TITLE OF PROJECT

Clinical and Morphologic Studies of the Human Dentition in Acquired and Inherited Metabolic Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Howell O. Archard, DDS, Chief, Diagnostic Pathology
Other Investigators: None
Cooperating Units: National Heart and Lung Institute, Endocrinology Branch
National Institute of Arthritis and Metabolic Diseases, Metabolic Diseases Branch
National Institute of Neurological Diseases and Strokes, Section on Child Neurology

NAME AND ADDRESS OF APPLICANT INSTITUTION
Branch: Experimental Pathology
Section: Diagnostic Pathology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Clinical and morphologic characteristics of the deciduous and permanent teeth of individuals affected with a wide variety of inherited or acquired metabolic diseases are studied. The gross and microscopic changes in the teeth are recorded, and correlations with the developmental events and general metabolic changes are undertaken.

Teeth removed from patients with metabolic disease who have been studied at the Clinical Center of the National Institutes of Health, comprise the major source of material, although specimens from outside sources are studied as well. Disorders currently under study include: Hereditary hypophosphatemia (Vitamin D-resistant rickets), hypophosphatasia, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism, Hurler's syndrome, diabetes insipidus, ectodermal dysplasia, chronic Vitamin D intoxication, infantile hypercalcemia, primary hyperoxaluria, porphyria, the Fanconi syndrome, cystinuria, acatalasia, etc.

Total Man Years: 1-1/4
Professional: 1/2
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard DDS	4/21/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-92(c)(70)

NIDR-EPB -005-(a)-70

TITLE OF PROJECT

Clinicopathologic Studies of Minor Salivary Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Thomas M. Tarpley, Jr., DDS
Other Investigators: Norman A. Cummings, Thomas M. Chused, and Robert O. Wolf
Cooperating Units: National Institute of Arthritis and Metabolic Diseases, Arthritis and Rheumatism Branch

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Experimental Pathology
Section : Diagnostic Pathology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Major and minor salivary glands from human and animal sources are studied by routine histological techniques and correlative histochemical, immunofluorescent, and electron microscopic procedures. Clinicopathologic studies of salivary glands in various disease states are undertaken. Diseases currently under study include Sjogren's syndrome, sarcoidosis, adenoid cystic carcinoma, lupus erythematosus and related connective tissue disorders.

Total Man Years: 2
Professional: 3/4
Other: 1¼

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M Tarpley Jr	4/21/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

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NATIONAL INSTITUTE OF DENTAL RESEARCH
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-88 (c) (66)

NIDR-EPB -006 -(c)-(66)

TITLE OF PROJECT

Oncological Research

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. James E. Hamner, III
Other Investigators: Dr. Fali S. Mehta
Chief, Basic Dental Research, Tata Institute of Fundamental Research, Bombay, India
Dr. Jens J. Pindborg, Chairman, Dept. Oral Pathology, Royal Dental College, Copenhagen, Denmark
Cooperating Units: Tata Institute of Fundamental Research, Royal Dental College

NAME AND ADDRESS OF APPLICANT INSTITUTION
Laboratory: Experimental Pathology
Section: Oncology
Location: N.I.D.R., N.I.H., Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Investigations underway or planned for the immediate future include: continued study of fibro-osseous jaw lesions, determination of oral cancer and premalignant oral lesions in rural Indian populations, collaboration as a collecting center for oral premalignant epithelial lesions with other World Health Organization designated centers, and study of oral cancer cases within the N.I.H. Clinical Center framework. Basic investigations of the carcinogenic activity of the ingredients of betel quid are being conducted on baboons under contract arrangement with the Southwest Foundation for Research & Education in San Antonio, Texas. These investigations are being carried out by Dr. Hamner.

Total Man Years: 1
Professional: 1/2
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James E Hamner III (Mrs.)	5-1-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-24

NIDR-HG-001-(a)-(54)

TITLE OF PROJECT

Genetics of Chemoreception Thresholds

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: K. S. Brown, Senior Surgeon, Human Genetics Branch, NIDR

Other Investigators: C. J. MacLean, Mathematical Statistician, Human Genetics Branch, NIDR

W. C. Leyshon, Biologist, Human Genetics Branch, NIDR

Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this study are to describe experimentally the variation between individuals in their detection thresholds for odors and tastes and to analyze the variation genetically and statistically to determine the nature of the components that contribute to this variation.

Several methods are being utilized. A statistical study of the components of variation in the detection thresholds of a variety of odors in a group of normal individuals is directed to identifying chemical groups that show common patterns of odor threshold. Family and twin studies are directed at detecting the contribution of genetic components of variability and at the study of any specific segregating traits.

Preliminary results have indicated that the components of variation include; a general factor which accounts for about 30 percent of variance and is positively correlated to all odors, specific factors related to ionization as acids or bases, and a residual factor which seems to rank unionized molecules according to molecular weight. Examination of the correlation between the thresholds of sibs, parents and children, do not provide evidence for a measurable genetic control of the thresholds of any of the tested pure compounds.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Kenneth S. Brown	4-24-72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-26

NIDR-HG-002-(a)-(62)

TITLE OF PROJECT

Discrimination and Segregation Analysis of Hereditary Deafness in the Students of the Clarke School for the Deaf

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: K. S. Brown, Senior Surgeon, Human Genetics Branch, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to study the distribution of cases of profound childhood deafness in families and in relationship to history of trauma or disease. By analysis of the segregation of deafness in families of different mating types the genetic contributions to deafness in childhood can be estimated.

The preliminary genetic analysis, treating the deafness as a clinically homogenous entity, has given results similar to other workers. Further studies are underway attempting to use clinical and genetic discrimination of different specific entities that the general analysis has shown to exist.

Techniques for detection of defects in the cochlear microphonic part of the hearing mechanism as developed in animals are being applied to humans.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Kenneth S. Brown	4-24-72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-27

NIDR-HG-003-(b)-(67)

TITLE OF PROJECT

Developmental Processes in Genetically Controlled Malformations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: K. S. Brown, Senior Surgeon, Human Genetics Branch, NIDR
Other Investigators: M. C. Johnston, Visiting Scientist, Human Genetics Branch, NIDR
H. A. Gross, Research Associate, Human Genetics Branch, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to describe the development of experimental animals with genetically produced congenital malformations, particularly those of the oral region, and to examine the interaction between the tissues of these animals in the developmental processes in order to determine the nature of the mechanism producing the genetic defect.

Several methods will be employed. A survey of mouse mutants is being undertaken to evaluate their oral structures in relation to those of the lines from which they arose. Mutants of specific interest are being collected, and colonies of these animals are to be developed as a basis for experimental study. Timed matings are being made to produce animals of known gestational age. Serial sacrifice and histological study will produce systematic documentation of the developmental processes. Comparative differences in rate of cleft palate and cleft lip and palate in inbred strains of mice are being studied as a response to changes in maternal environment during different stages of pregnancy.

Assays of hormonal levels during pregnancy and during teratogenic stimulation are being carried out to evaluate the effects of hormones on development of defects.

Total Man Years: 3 1/4
Professional: 1
Other: 2 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	K. S. Brown	4-24-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-28

NIDR-HG-004-(b)-(70)

TITLE OF PROJECT

Embryological Studies of Facial Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: M. C. Johnston, Visiting Scientist, Human Genetics Branch, NIDR

Other Investigators: A. Bhakdinaronk, Visiting Fellow, Human Genetics Branch, NIDR
Y. C. Reid, Biologist, Human Genetics Branch, NIDR
K. S. Brown, Senior Surgeon, Human Genetics Branch, NIDR
J. Goggins, Sr. Dental Surgeon, Experimental Pathology Branch, NIDR

Cooperating Units: R. D. Hazelton, Hospital for Sick Children, Toronto;
D. N. Noden, Washington University; A. J. Steffek, American Dental Association; R. Peach, University of North Carolina

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The objectives of this project are to study the migrations, interactions and derivatives of neural crest and other primordia involved in normal embryological facial development and to use the information for the study of facial malformations. The normal aspects of the study are conducted primarily on avian and rodent embryos, the latter developing in organ culture. Various histological techniques are used. These include radioautography (and other procedures for following the migrations of cells) and histochemistry, as well as fluorescence, phase contrast and electron microscopy. The embryogenesis of spontaneous and induced malformations, particularly cleft lip and palate, is being studied in the mouse. Efforts are being made to influence the abnormal processes leading to "spontaneous" clefts through manipulation of environmental factors.

Total Man Years: 2 3/4
Professional: 2 1/2
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Malcolm C Johnston	April 25/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-None

NIDR-HG-005-(a)-(72)

TITLE OF PROJECT

Radioimmunoassay of Hormones

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: H. A. Gross, Research Associate, Human Genetics Branch, NIDR
Co-Investigator: K. S. Brown, Senior Surgeon, Human Genetics Branch, NIDR
Cooperating Units: H. Ruder, Reproductive Research Branch, NICHD
M. Lipsett, Reproductive Research Branch, NICHD

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Developmental Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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It has been shown that steroids conjugated to bovine serum albumin (BSA) or other proteins are antigenic and may be used to produce specific antibodies which can be used in radioimmunoassay procedures. We have developed a simple and reliable radioimmunoassay for plasma corticosterone determination in mice which requires 40 µl of plasma. Our antiserum was produced in rabbits immunized with corticosterone-21-hemisuccinate conjugated to BSA.

Plasma corticosterone from mice is readily measured by directly assaying aliquots of a methylene chloride extract of plasma. Linear standard curves were obtained and a series of corticosterone determinations performed to determine normal values of corticosterone in A/Jax mouse plasma before and after ACTH stimulation of 8.1 µg% ± .41 (S.E.) and 44.3 ± 3.8 (S.E.) respectively. After dexamethasone suppression plasma corticosterone values were 0.8 ± .38 (S.E.). Our method shows good precision, accuracy and specifity. The mean and standard error plasma corticosterone levels in mice were similar to those reported by other investigators using different methods.

We are measuring plasma cortisol levels in mice with an antibody produced in rabbits by Dr. Henry Ruder and Dr. Mortimer Lipsett. In the immediate future we will be determining plasma T_4 and T_3 levels with a similar antibody radioimmunoassay method.

Total Man Years: 1 1/4
Professional: 3/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Howard Allen Gross, M.D.	4/25/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-31

NIDR-HG-006-(b)-(67)

TITLE OF PROJECT

Genetic Analyses in Human Populations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: C.J. MacLean, Mathematical Statistician, Human Genetics Branch, NIDR
Co-investigator: J.D. Niswander, Dental Director, Human Genetics Branch, NIDR
Other Investigators: W.C. Leyshon, Biologist, Human Genetics Branch, NIDR
B.Y. Iba, Geneticist (Human Medical), Human Genetics Branch, NIDR
R. Singleton, Computer Systems Analyst, Human Genetics Branch, NIDR
Cooperating Units: M.S. Adams, University of Rochester
P.L. Workman, University of Massachusetts

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to determine which particular factors are influencing the pattern of genetic variation in any population at a given time. Of special interest are such factors as assortative mating, selection, population intermixture, and population size; (2) to develop suitable methods for the analysis of intra- vs inter-population differences. Particularly important are those techniques which permit an assessment of the relative stability of genotypic distributions over space and time. (3) To investigate the relationship of birth and death rates to population size and age structure. This work concentrates on the differences within and between various populations with particular emphasis on the American Indian.

Total Man Years: 2 1/4
Professional: 1 3/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: J.D. Niswander

DATE: 4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-29

NIDR-HG-007-(a)-(58)

TITLE OF PROJECT

Congenital Malformation and Birth Characteristics of American Indians

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: J. D. Niswander, Dental Director, Human Genetics Branch, NIDR
Other Investigators: B. Y. Iba, Geneticist (Human Medical), Human Genetics Branch, NIDR
R. Singleton, Computer Systems Analyst, Human Genetics Branch, NIDR
Cooperating Units: M. V. Barrow, J. Hillis Miller Health Center, University of Florida

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Human Genetics
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study is based on approximately 45,000 clinical newborn records from forty-six Public Health Service Hospitals to ascertain the total (at birth) frequency of congenital malformation among American Indians as well as frequencies of specific major defects. These data are compared to those obtained from other Mongoloid and Caucasoid populations. A major objective of this study is to examine the effect of tribal background and Caucasion admixture on variation in malformation rates. Several medical, culture and socio-economic variables are included as indicators of environmental effects. Birth weight and twinning rates are examples of other birth characteristics being analyzed.

Total Man Years: 1 3/4
Professional: 1 1/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jerry D. Niswander	4/24/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-30

NIDR-HG-008-(a)-(63)

TITLE OF PROJECT

Genetic Studies of Oral Diseases, Anomalies and Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: J. D. Niswander, Dental Director, Human Genetics Branch, NIDR
Cooperating Units: J. A. Sofaer, Department of Genetics, University of Cambridge
C. S. Chung, School of Public Health, University of Hawaii

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies are being conducted on Hawaiian school children and among various Amerindian tribes in an attempt to clarify the relative role of genetic and environmental factors in certain oral conditions. These studies have as their objective: (a) to determine the effects of inbreeding and hybridization on malocclusion and dental caries; (b) to assess the role of environment in malocclusion--specifically has the frequency, type and severity of malocclusion changed over time, and if so, can the changes be related to socioeconomic status and changing cultural patterns; (c) to assess the correlation between relatives in malocclusion; and (d) to elucidate genetic mechanisms involved in morphological variations of the teeth.

Total Man Years: 3/4
Professional: 1/2
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jerry D. Niswander	4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-29

NIDR-HG-009-(a)-(58)

TITLE OF PROJECT

Characteristics of Families with Oral Clefts

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: J. D. Niswander, Dental Director, Human Genetics Branch, NIDR
Co-investigator: M. C. Johnston, Visiting Scientist, Human Genetics Branch, NIDR
Other Investigators: B. Y. Iba, Geneticist (Human Medical), Human Genetics Branch, NIDR
R. Singleton, Computer Systems Analyst, Human Genetics Branch, NIDR
C. J. MacLean, Mathematical Statistician, Human Genetics Branch, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Human Genetics
Section: Population Genetics
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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This project is designed to determine 1) if there are physical stigmata particularly changes in facial morphology associated with oral clefts, which are familial in nature and may be useful in clarifying the role of genetic (and environmental) factors in the etiology and pathogenesis in these anomalies. Of particular interest is the study of various characteristics obtained from cephalometric radiographs of affected individuals as well as their "normal" relatives including twins. Another objective 2) is to develop methods to identify and classify heterogeneous subtypes of oral clefts and to identify individuals who are genetically at high risk. Other aspects of this project include 3) the relationship of sex ratio and fetal mortality to genetic predisposition. 4) Work is also in progress on the development of new genetic models applicable to oral clefts and the extension of techniques of segregation analysis.

Total Man Years: 2 1/4
Professional: 1 1/2
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Jerry D. Niswander

DATE: 4/24/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-13 NIDR-LB -101-(b)-52

TITLE OF PROJECT

Structural Studies on Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Karl A. Piez, Chief, Laboratory Biochemistry, NIDR
Other Investigators: Dr. Alfred Quattrone, Staff Fellow, Protein Chem. Section, LB, NIDR
Dr. Barbara Doyle, Guest Worker, " " " " "
Dr. Dennis Torchia, Guest Worker, " " " " "
Cooperating Units: National Bureau of Standards

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the long range purpose of this project to study the structure of collagen at various levels and correlate with function. The topics of present interest are:

1. The role of the amino-terminal nonhelical regions of the α chains of collagen fibrillogenesis. Linear and lateral associations of collagen molecules in the collagen fibril must be controlled by structural features of the molecule. The role of the amino-terminal regions is being examined by studying interactions of peptides containing these regions with collagen.
2. The purpose of hydroxyproline in collagen structure. Nonhydroxylated collagen (protocollagen) will be isolated and its properties compared with collagen.
3. The conformation of collagen. Nuclear magnetic resonance studies on well characterized peptides from collagen should contribute to an understanding of several structural features such as side chain interactions and hydrogen bonding.

Total Man Years: 6 1/4
Professional: 2 1/4
Other: 4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Karl A. Piez	5/8/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.:NIDR-14

NIDR-LB -102-(b)-62

TITLE OF PROJECT

The Chemistry of Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Karl A. Piez, Chief, Laboratory Biochemistry, NIDR

Other Investigators: Dr. Herbert Evans, Staff Fellow, Protein Chem. Sect., LB, NIDR
Dr. Alan Nicholls, Visiting Fellow, " " " " "

Cooperating Units: Dept. of Biochemistry, Univ. of Washington, Seattle (Dr. Paul Bornstein)

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The broad aim of this project is to determine the covalent structure of collagen including both amino acid sequence and covalent interchain cross-links. Differences that can be related to tissue, species, developmental stage and connective tissue pathology are of particular interest. Currently active aspects of the study include amino acid sequencing of cyanogen bromide peptides of rat skin collagen, the isolation and characterization of multichain peptides containing cross-links, and the development of methods to scan small samples of collagen for differences.

Total Man Years: 3 1/4
Professional: 1 1/4
Other: 2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Karl A Piez	5/8/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 17

NIDR-LB -201-(b)-62

TITLE OF PROJECT

The Chemistry and Biosynthesis of Connective Tissue

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. G. R. Martin, Chief, Connective Tissue Section, LB, NIDR

Other Investigators: Dr. David Rowe, Clinical Associate; Dr. Barbara Smith, Research Chemist, Dr. D. J. Lichtenstein, Guest Worker, Dr. Peter Byers, Research Associate, Dr. Lawrence G. Raisz, Guest Worker, Dr. Thomas Nigra, Clinical Associate, NCI, Dr. Michael Sussman, Guest Worker

Cooperating Units: Genetics Department, Johns Hopkins Medical School
Dermatology Branch, NCI
Department of Orthopedic Surgery, Johns Hopkins Medical School

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Md.

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Collagen and elastin are two of the major constituents of connective tissues. The purpose of this project is to study their metabolism in normal and disease states and the cellular control of their formation. Currently active aspects of the project include the isolation and characterization of procollagen, elucidation of the conversion of procollagen to collagen, the study of inherited diseases of connective tissue utilizing cells in culture, and examination of the effect of inflammation on collagen metabolism.

Total Man Years: 9
Professional: 6
Other: 3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Geze R Martin	5/9/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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HEALTH, EDUCATION, AND WELFARE
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Prepared for the Science Information Exchange.

Not for publication or publication reference.

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 18

NIDR-LB -202-(b)-61

TITLE OF PROJECT

Studies on Chemotaxis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Elliott Schiffmann, Chemist, Connective Tissue Section, LB, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is proposed to gain insight into the biochemical processes of cell migration along a chemical gradient. Cells such as leucocytes, bacteria, and the slime mold all have the property of responding to their environment in this manner. We are concentrating upon the isolation and characterization of a material exuded from an E. coli strain which is chemotactic for leucocytes. Such material also appears to affect an enzyme system involved in the chemotactic response of the slime mold. In addition a complement derived factor has been shown by others to attract leucocytes. It is hoped that by studying the interaction of these substances with the white cell and its components some explanation on the directed movement of cells might be forthcoming.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	E Schiffmann	5/9/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 19

NIDR-LB -301-(b)-72

TITLE OF PROJECT

Comparative Aspects of the Mammalian Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. S. I. Chung, Senior Staff Fellow, Enzyme Chemistry Section, LB, NIDR

Other Investigators: Dr. J. E. Folk, Chief, Enzyme Chemistry Section, LB, NIDR

Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Enzyme Chemistry
Location: NIDR, NIH, Bethesda, Md.

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the purpose of these studies to isolate and characterize members of an important group of enzymes, termed transglutaminases, that catalyze the formation of covalent cross-links between protein molecules. Efforts in this laboratory have served to define three distinct classes of these enzymes in guinea pig and human tissues and organs. Of particular interest are the roles of the individual transglutaminases in blood coagulation, wound healing, cell membrane formation, proper cross-linking of hair proteins, and covalent attachment of biological amines to proteins.

Biological control mechanisms, including zymogen forms, essential metal ion requirements and specific antibody-antigen-type binding, are under investigation. Subunit structure are evident and are under study. Mechanism, active site, and specificity studies are in progress.

Total Man Years: 3
Professional: 1 3/4
Other: 1 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	S. I. Chung	5/9/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 19 NIDR-LB -302-(h)-52

TITLE OF PROJECT

Chemical, Stereochemical and Conformational Aspects of Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. M. A. Gross, Staff Fellow, Enzyme Chemistry Section, LB, NIDR
Other Investigators: Dr. J. E. Folk, Chief, Enzyme Chemistry Section, LB, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Enzyme Chemistry
Location: NIDR, NIH, Bethesda, Md.

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A series of substrates and analogs of substrates for transglutaminase have been synthesized and employed to gain information concerning the structural and environmental features of the active site areas of these enzymes. It is the purpose of these studies to relate the structures of the enzymes to their catalytic function. Future studies will include examination of the effects of metal ion activation on the environmental nature of the active sites, conformational changes induced by metal ion and substrate binding, and comparison of the physical and chemical properties of the catalytic regions of various transglutaminases.

Total Man Years: 1 1/2
Professional: 1 1/2
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Marvin A. Gross	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-21

NIDR-LB -401-(b)-62

TITLE OF PROJECT

Cell Growth Studies in Normal and Abnormal Subjects

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. H. L. Cooper, Chief, Cell Biology Section, LB, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Biochemical processes which regulate the growth of human lymphocytes in vitro are being studied. The RNA metabolism of resting and growing lymphocytes is being investigated in order to clarify growth-related alterations in the synthesis, processing and degradation of various RNA species.

Newly synthesized ribosomal RNA was found to be rapidly degraded, in large proportion, in resting lymphocytes. This wastage was rapidly reversed on growth stimulation. The control of this wastage depends upon the production of a ribosomal protective protein. The points of action of this protein in RNA metabolism are being investigated.

Total Man Years: 3 1/4
Professional: 1/2
Other: 2 and 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Herbert L. Cooper	5/9/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-22

NIDR-LB -402-(b)-67

TITLE OF PROJECT

RNA Synthesis in Animal Cells

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. R. Stern, Medical Officer, Cell Biology Section, LB, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Research will continue in the area of metabolism of minor RNA species unique to the mammalian cell, particularly those synthesized in the presence of actinomycin. Normal and known RNA virus infected cells will be used as controls in the search for evidence of unique RNA species in viruses. Synthesis of the RNA tumor virus and its relationship to the minor species of RNA synthesized in the presence of actinomycin will be examined. A byproduct of this investigation will be characterization of other RNA structures in the normal and abnormal mammalian cell. The classes of RNA in mammalian cells will be related to the various RNA polymerases of the cell.

The enzyme in serum which hydrolyzes double-stranded RNA will be further purified and characterized. The enzyme will be used as a tool to study the structure of the intermediates in the replicative cycle of RNA viruses.

Total Man Years: 1/2
Professional: 1/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	R Stern	5/9/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-23

NIDR-LB -403-(b)-69

TITLE OF PROJECT

Studies in Cellular Immunology

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. G. D. K. Hopper, Research Associate, Cell Biology Section, LB, NIDR
Other Investigators: Dr. H. L. Cooper, Chief, Cell Biology Section, LB, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A study of the processing of antigen by macrophages during in vitro lymphocyte growth induction by antigen. The steps by which the macrophage renders antigen stimulatory for lymphocytes are being sought. This project will be terminated at the end of FY 1972.

Total Man Years: 2 1/2
Professional: 1 1/2
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David G. Hopper M.D.	5/9/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotioted Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LB -404-(b)-72

TITLE OF PROJECT

Studies of Ribosomal Proteins in Mammalian Cells

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. S. Bradbury, Staff Fellow, Cell Biology Section, LB, NIDR
Other Investigators: Dr. H. Cooper, Chief, Cell Biology Section, LB, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Initial stages of this project will involve isolation and partial characterization of proteins from ribosomes and ribosomal subunits of HeLa cells and normal human lymphocytes.

Total Man Years: 3/4
Professional: 3/4
Other: None

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Shelby L. Bradbury	5/9/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-LB-405-(b)-72

Prev. Ser. No. None

TITLE OF PROJECT

In Vitro Synthesis of Collagen and Characterization of the Messenger RNA for Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. R. Stern, Medical Officer, Cell Biology Section, LB, NIDR
Other Investigators: Dr. Kathy Benveniste, Staff Fellow, Cell Biology Section, LB, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biochemistry
Section: Cell Biology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this project is to synthesize collagen in a cell-free system using heterologous sources of ribosomes and protein synthesizing factors. Isolation and characterization of the messenger RNA for collagen is being attempted. Tissue specific factors for optimal collagen synthesis are being sought including tRNA and protein initiation factors. In vitro synthesis of hemoglobin and viral proteins are being used for comparative analysis.

The acylation of proline, glycine and arginine to their respective tRNAs from collagenous and non-collagenous tissues is being studied. The isoacceptor tRNAs for these amino acids are being separated and their interaction with their respective amino acyl synthetases is being examined. The RNA codewords for each tRNA will be established by ribosome binding assays. Results will be coordinated with the cell-free synthesis of collagen.

Total Man Years: 2 1/4
Professional: 1 1/2
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	R Stern	5/9/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -001-(h)-(72)

TITLE OF PROJECT

Ultrastructural Studies of Secretory and Post Secretory Ameloblasts in Normal Rats and in Animals Treated with Tetracycline Hydrochloride

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. M. U. Nylen, Chief, Laboratory of Biological Structure
Co-principal Investigator: Dr. J. Westergaard, Visiting Associate
Cooperating Unit: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The morphology and enzyme contents of secretory and post-secretory ameloblasts from continuously growing rat incisors are under study. Normal 4 day old animals or 4 day old animals injected with either 50 or 100 mg/kg tetracycline hydrochloride of body weight are sacrificed by perfusion through the heart with a fixative. Half of the teeth are processed directly for observation in the electron microscope while the other half is decalcified prior to processing. Enzymes presently under investigation are acid phosphatase and thiamine pyrophosphatase.

Total Man Years: 3 1/4
Professional: 2
Other: 1 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Marie U. Nylen	5/4/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -002-(b)-(68)

TITLE OF PROJECT

Biophysical Studies of the Relationship of Cells and Matrix to the Mechanism of Bone and Dentin formation prior to actual Crystal Formation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. P. D. Frazier
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies proposed are intended to determine the exact location of the non-crystalline ash content of collagen fibrils relative to the band structure of the fibril. This region may be responsible for accumulating additional inorganic constituents as part of the mechanism by which collagen becomes calcified. An attempt will be made to detect such an accumulation using low-temperature microincineration methods in conjunction with electron probe analysis and electron microscopy.

Studies will also be undertaken to further clarify the potassium pyroantimonate precipitation reaction in vesicles formed in the Golgi region of odontoblasts.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Paul D. Frazier	MAY 4, 1972

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-70

NIDR-LBS -003-(b)-(68)

TITLE OF PROJECT

Ultrastructure and Cytochemistry of Salivary Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. A. R. Hand
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The ultrastructure and cytochemistry of the rat parotid gland is being studied. Primary emphasis is placed upon the role of lysosomes in the physiology of the acinar cells. The glands are examined after acute starvation, starvation-refeeding, or injection of isoproterenol. The evidence gathered to date indicates that lysosomes function in the segregation and digestion of secretory material when the stimulus for its discharge from the cells is removed. In addition, lysosomes may be involved with the retrieval and degradation of secretory granule membranes following discharge of the granule contents.

Total Man Years: 1 3/4
Professional: 3/4
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Arthur R Hand	May 4, 1972

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-LBS -004-(b)-(70)

Prev. Ser. No. NIDR-71

TITLE OF PROJECT

The Fine Structure of Intercellular Junctions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. A. Hand
Other Investigators: Dr. S. Gobel, Neural Mechanisms Section, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The structure and function of intercellular junctions is being studied utilizing electron microscopy, extracellular tracer molecules, and freeze-etch replication. Initial studies were concerned with the structure of the septate and gap junctions of Hydra. The studies are now being extended to the mammalian desmosome and synapse.

Total Man Years: 3/4
Professional: 1/4
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	William R Hand	May 4, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -005-(b)-(71)

TITLE OF PROJECT

Ultrastructure of Salivary Glands of Maturing and Aging Hamsters (Mesocricetus auratus)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. H. Flon, USPHS Special Research Fellow, Guest Worker, NIDR
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The form, organization, and orientation of the cellular organelles and inclusions of (1) the acinar cells of the sublingual, submandibular, and parotid glands, (2) the convoluted granular tubules of the submandibular gland, and (3) the intercalated duct cells of the parotid gland during their respective periods of cytodifferentiation and maturation and in the aging animal are being studied.

Electron microscopic observations are made on chemically-fixed tissues, preserved by the dual-fixation procedure of glutaraldehyde and osmium (Sabatini et al.: J. Cell Biol. 17:19, 1963) and on tissues fixed by freezing.

Ultrastructural localization of secretory substances during the aforementioned periods will be accomplished by (1) radioautographic procedures with C^{14}-labeled tryptophan or tyrosine for glycoprotein substances and H^3-labelled glucose or glucosamine and radioactive sodium sulfate for acid mucosubstances and (2) cytochemical methods with the periodic acid oxidation-silver methenamine method of Rambourg (J. Histochem. and Cytochem. 15:409, 1967), the modified Hale's dialyzed iron method of Wetzel et al. (J. Cell Biol. 30:299, 1966), or the colloidal thorium method of Revel (J. Microscopie 3:535, 1964), with and without prior digestion with sialidase and pepsin.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Helen Flon	5-4-72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72

NIDR-LBS -006-(b)-(68)

TITLE OF PROJECT

Studies on Inhibition of Plaque Formation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. H. A. Bladen, Chief, Structural Interactions Section
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biological Structure
Section: Structural Interactions
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The general objective of this project is to determine the possibility of biological inhibition of in vitro plaque formation by oral streptococci or diphtheroids implicated in the initiation of caries or periodontal disease. This encompasses perfecting and evaluating screening procedures which detect biologically produced plaque inhibitory substances. These substances, when found will be isolated and characterized.

Total Man Years: 2 1/4
Professional: 1
Other: 1 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Howard A. Bladen	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74

NIDR-LBS -007-(b)-(69)

TITLE OF PROJECT

Studies on Oral Filamentous Microorganisms Implicated in Periodontal Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. G. J. Hageage, Jr.

Other Investigators: Dr. H. A. Bladen, Chief, Structural Interactions Section
Dr. L. A. Thompson and Dr. P. H. Keyes, Caries Prevention and Research Branch, NIDR

Cooperating Units: Dr. J. M. Tanzer, Caries Prevention and Research Branch, VA Hospital, Newington, Conn.

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biological Structure
Section: Structural Interactions Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The general objectives of this project involve the structure, taxonomy, epidemiology, immunology, and pathogenicity of gram-positive oral filamentous bacteria of rodent and human origin implicated in the initiation of periodontal pathosis. Present studies involve the evaluation of direct fluorescent antibody staining of micro-colonies and their subsequent identification by vertical ultraviolet illumination as a method for the detection and rapid identification of these organisms growing on primary isolation plates.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	George J. Hageage Jr.	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-LBS -008-(b)-(69)

Prev. Ser. No. NIDR-77

TITLE OF PROJECT

X-ray Diffraction Study of Turkey Leg Tendon

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. D. R. Lundy, Staff Fellow
Other Investigators: Dr. E. D. Eanes, Chief, Molecular Structure Section
Mr. G. N. Martin, Chemist
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Several different methods of x-ray line broadening analysis were applied to a determination of the crystal size and perfection of mineralized turkey leg tendon in order to compare the methods to each other and to previous results. Results show that the methods give similar results if differences in the mathematical definitions of size and strain are considered. Single peak methods, necessary in the study of synthetic apatites compare favorably to multiple peak methods. Therefore synthetic apatite systems can be studied as mineralization models.

Hydration studies on calcified and non-calcified tendon are being analyzed by weight gain studies and by increases in spacing of the 11 Å diffraction line. Through humidities of 84%, both the calcified and non calcified tendon show similar increases in the side chain spacing. While the non calcified tendon has a greater increase in weight, if a 35% content of non adsorbing mineral is assumed, the weight increases are similar. These observations would seem to indicate that the mineral occupies very few sites of those available for water adsorption. The remaining humidities 90-100%, according to the literature, should be the region where differences would be revealed.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Donald R. Lundy	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -009-(b)-(71)

TITLE OF PROJECT

Hydrazine Deproteinated Bone Mineral: Physical and Chemical Properties

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. J. D. Termine, USPHS Special Research Fellow, Guest Worker
Other Investigators: Dr. E. D. Eanes, Chief, Molecular Structure Section and Dr. D. J. Greenfield
Cooperating Units: Dr. R. A. Harper, Department of Physics, Rensselaer Polytechnic Institute, Troy, N. Y.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Purified hydrazine reagent is used to completely deproteinate both young and mature rodent bone. This deproteination is carried out with gentle heating in a rapid and quite simple manner, during which the resultant bone mineral becomes extensively dehydrated. The anorganic bone produced by this method was found to contain less than 0.3 percent nondialyzable protein by direct chemical analysis. Control studies have indicated that no major changes in either the physical or chemical properties of the reacting mineral phase occur during the hydrazine deproteination procedure. The complete chemical, physicochemical and morphological characterization of deproteinated bone mineral is currently under investigation.

Total Man Years: 3/4
Professional: 1/2
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	John D. Termine	5/4/72

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 75

NIDR-LBS-010-(b)-(70)

TITLE OF PROJECT

Electron Microscopic Study of the Formation and Conversion of Amorphous Calcium Phosphate

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. E. D. Eanes, Chief, Molecular Structure Section
Other Investigators: Dr. J. D. Termine, Dr. M. U. Nylen
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Studies are currently underway to establish the morphology of amorphous calcium phosphate (ACP) during its formative stage and the alterations in this morphology during its conversion to crystalline apatite. Also being examined are the spatial relationships between the ACP precursor and the final crystalline phase. Particular attention is being directed to elucidating the structural state of ACP in aqueous solution. Since the ACP must be dry for electron microscopy, procedures are being investigated that will minimize the shrinkage and distortion that may accompany the drying of ACP.

Total Man Years: 1 1/2
Professional: 3/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	E. D. Eanes	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -011-(b)-(71)

TITLE OF PROJECT

Comparative Chemistry of Amorphous and Apatitic Calcium Phosphate Preparations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. J. D. Termine, USPHS, Special Research Fellow, Guest Worker
Other Investigators: Dr. E. D. Eanes, Chief, Molecular Structure Section
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Unwashed samples of Amorphous Calcium Phosphate (ACP) contain an irreplaceable labile fraction rich in Acid Phosphate and low in Ca/P ratio which is irreversibly lost during washing. Native ACP precipitated between pH 6.6 and 10.6 varies in Ca/P molar ratio from 1.15 to 1.50 and in HPO_4^{-2}/total P from 33.0 to 10.1 percent. Thus, the amorphous calcium phosphates are recognized as a family of noncrystalline salts having variable chemical but identical physicochemical properties.

At physiological pH, ACP converts to small platy crystals having apatitic diffraction patterns. These crystals contain large amounts of readily replaceable surface HPO_4^{-2} ions. Washing excess phosphate from the crystals procudes other chemical alterations. In all cases, the crystallites remain poorly defined structurally and no definitive interpretation of their submolecular detail is possible.

Total Man Years: 1
Professional: 1/4
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	John D. Termine	5/4/72

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-76

NIDR-LBS -012-(b)-(68)

TITLE OF PROJECT

Chemical Studies of Bone Mineral and Its Synthetic Analogues

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. D. J. Greenfield, Research Associate
Other Investigators: Dr. E. D. Eanes, Chief, Molecular Structure Section
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Having established the composition of and factors affecting the formation of amorphous calcium phosphates prepared from carbonate containing solutions, attention is currently being focused on the kinetics and compositional changes which occur on conversion of these amorphous precipitates to hydroxyapatite. Specific factors under study include the effect of the carbonate content of the amorphous material, pH, and extraneous ions on the time required for conversion to crystalline apatite, the changes in acid phosphate and carbonate content following conversion as well as the question of carbonate interference with acid phosphate analysis of certain calcium phosphate species.

An additional series of experiments has been devised to determine the acid phosphate content of animal bones. Preliminary results indicate that previous studies have not used optimal conditions to examine this question and therefore a detailed analysis of heating conditions for the conversion of acid phosphate to pyrophosphate has been undertaken for both rodent bones and synthetic preparations. This data will then be used to re-examine the effects of growth and aging on the acid phosphate content of bone mineral.

Total Man Years: 1 1/4
Professional: 1
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	David Greenfield	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-69

NIDR-LBS -013-(b)-(68)

TITLE OF PROJECT

Infrared Spectroscopy of Human Amyloid Fibrils and Immunoglobulin Proteins

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. J. D. Termine, USPHS, Special Research Fellow, Guest Worker
Other Investigators: Dr. E. D. Eanes, Chief, Molecular Structure Section
Cooperating Units: Dr. D. Ein and Dr. G. G. Glenner, Immunology Branch, National Cancer Institute and Laboratory of Experimental Pathology, National Institute of Arthritis and Metabolic Diseases

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Infrared spectroscopy has confirmed the presence of the extended antiparallel-β-pleated sheet conformation in human amyloid fibrils. This three dimensional protein configuration is generally enhanced by acidic solution conditions. A combined x-ray diffraction and infrared spectroscopy (Amide I and Amide V absorption bands) study of the immunoglobulin molecule for solid state β-structure revealed that both isolated heavy chains and Bence Jones proteins exhibit some β-pleated sheet content upon acid and/or heat treatment. Moreover, it was the variable portions of these immunoglobulin heavy and light chains which were most easily capable of assuming a solid state antiparallel-β-pleated sheet conformation. The filamentous variable fragments of immunoglobulin light chains were most like amyloid in their physicochemical properties. These results are consistent with the hypothesis that in vivo, amyloid fibrils may result from an intralysosomal catheptic digestion of either whole immunoglobulin molecules or isolated light chains.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	John D. Termine	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-69

NIDR-LBS -014-(b)-(70)

TITLE OF PROJECT

X-ray Diffraction Study of the Influence of Electrolytes on Lamellar Lecithin Mesophases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. E. D. Eanes, Chief, Molecular Structure Section
Other Investigators: None
Cooperating Units: Dr. M. H. Gottlieb, Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The effect of added electrolytes on the thickness of phospholipid bylayers in lecithin-water mixtures is being investigated by small-angle x-ray diffraction techniques. Electrolytes being investigated are LiCl, NaCl, Na_2SO_4, CsCl, KCl, $CaCl_2$, and HCl at 1.0 N concentrations. The effect of electrolytes on the maximal amount of solution that can be mixed with lecithin before phase separation occurs is also being determined.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	E. D. Eanes	5/4/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-79

NIDR-LBS -015-(b)-(63)

TITLE OF PROJECT

Infrared and Raman Spectroscopic Studies of Teeth and Bones and Related Synthetic Compounds

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Mr. Bruce O. Fowler
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The main objective is to determine compositional and structural details of the inorganic phase in teeth and bones. Infrared (4000-60 cm^{-1}) and Raman spectroscopy as well as chemical methods are employed in these studies. Methods are devised for preparation of synthetic calcium apatites of controlled physical properties (crystal size and perfection) and chemical composition containing biologically relevant constituents, e.g., hydroxyl, fluoride, chloride, carbonate, water and acid phosphate. The vibrational spectra of these apatites and related compounds are assigned and characterized. Isotopically enriched apatite analogs are prepared to facilitate spectral assignments. The spectroscopic assignments and supplemental spectral data (temperature dependency and polarization) are utilized to establish compositional and structural details of the apatites which include the type and geometry of ions, the site or number of sites occupied by ions, orientation of ions, chemical bonding and interactions of ions and semi-quantitative estimations of constituents present. The results of findings for the controlled apatite system are related to the inorganic phase in calcified tissues.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Bruce O. Fowler	4 May 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-80

NIDR-LBS -016-(b)-(63)

TITLE OF PROJECT

Exogenous and Endogenous Factors Affecting Normal Development of the Oral Facial Region

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. C. T. G. King, Chief, Experimental Pharmacology Section
Other Investigators: Miss A. L. Wilk
Cooperating Units: Dr. H. McClure, Yerkes Primate Center, Atlanta, Georgia

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The congenital malformation of cleft palate is being induced at will with a variety of chemical agents (Lathyrogens, Benzhydrilpiperazines, Vitamin A, etc.) in a number of different mammalian species. Interspecies differences in metabolism and teratogenic response are under investigation. In addition fetal outcome from prolonged versus acute drug administration is studied.

A collaborative study with Dr. H. McClure (Yerkes Primate Center, Atlanta, Georgia) has been designed to determine the value of the rhesus monkey as an animal model in teratology.

Total Man Years: 1 3/4
Professional: 1
Other 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research		5 4/27

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-80

NIDR-LBS -017-(b)-(63)

TITLE OF PROJECT

Metabolism and Mechanism of Action of Teratogens, Norchlorcyclizine, β-Aminopropionitrile and Thalidomide

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Miss A. L. Wilk
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Norchlorcyclizine and β-aminopropionitrile are potent teratogens that induce a high percentage of cleft palate. These compounds are being used in a variety of animal species in order to delineate their mode of action and the etiology of the malformation.

Thalidomide is teratogenic in the rat only when it is applied directly on the amniotic sack of the developing embryo. This technique is being utilized to study the pharmacodynamics of thalidomide directly on the embryo.

Total Man Years: 1 1/2
Professional: 1
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Ann L. Wilk	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-80A

NIDR-LBS -018-(b)-(70)

TITLE OF PROJECT

Changes in the Macromolecular Constituents of Embryonic Connective Tissue in Experimentally Induced Cleft Palate of the Rat and Fetus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Robert M. Pratt, Jr.
Other Investigators: Dr. C. T. G. King, Dr. John Hassell and Miss Ann Wilk
Cooperating Units: Drs. Gary Smiley, William Waddell and Gerald Mechanic, Dental Research Center, University of North Carolina

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Studies in the synthesis of proteins, including collagen, and acid mucopolysaccharides in embryonic tissue as a whole, and the isolated secondary palate are being conducted in normal and cleft palate embryos in order to delineate the etiology of the malformation. In these studies, standard biochemical, histological and autoradiographic techniques are being used. The malformation of cleft palate is being induced by specific agents, such as Beta aminopropionitrile. The development of the malformation is being followed by in vivo and in vitro techniques in order to determine the role that acid mucopolysaccharides, glycoprotein and collagen may play in palatal rotation and fusion.

Total Man Years: 1 3/4
Professional: 1
Other: 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Robert M. Pratt, Jr.	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

NIDR-LBS -019-(b)-(72)

TITLE OF PROJECT

Quantitative Changes in Macromolecular Components in Palatal Shelf Tissue During Palatal Growth and Epithelial Fusion in the rat Fetus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. John R. Hassell

Other Investigators: Dr. C. T. G. King, Chief, Experimental Pharmacology Section, Dr. Robert Pratt and Miss Ann Wilk

Cooperating Units: Dr. Stanley Cohen, Department of Biochemistry, School of Medicine, Vanderbilt University, Nashville, Tennessee 37203

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Biological Structure
Section: Experimental Pharmacology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Current studies are designed to provide insight into certain biochemical processes involved in palatal shelf growth and fusion. Growth will be measured by determining the rates of synthesis, accumulation and breakdown of DNA, RNA and protein in palatal shelf tissues obtained from control animals as well as animals treated with teratogenic agents. Epithelial fusion and breakdown will be evaluated at the ultrastructural level and will also involve the use of stains specific for protein and carbohydrates not employed in previous studies. In addition, experiments will be conducted to determine if the Epidermal Growth Factor (provided by Dr. Stanley Cohen) will act as a teratogenic agent by blocking epithelial fusion or epithelial breakdown in vivo and in vitro models.

Total Man Years: 1 1/2
Professional: 1
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	John R. Hassell	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. - 61 (65)

NIDR-LMI -001-(b)-(65)

TITLE OF PROJECT

The Role of Complement in the Inflammatory Response

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Stephan E. Mergenhagen
Other Investigators: Dr. Ralph Snyderman, Dr. James David Small
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Laboratory of Microbiology & Immunology
Section:
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this work are 1) to clarify the various pathways by which complement may be activated by endotoxins and immune complexes and 2) to characterize biologically-active cleavage products of the complement systems which are involved in the initiation of the acute inflammatory response. This entails in vitro models for studying such phenomenon as leukocyte chemotaxis, platelet degranulation and histamine release from mast cells. In addition, investigations will be initiated to study the kinetics of inflammatory cell accumulations in animals genetically deficient in certain of the complement proteins.

Total Man Years: 6 1/2
Professional: 2 1/2
Other: 4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stephan E. Mergenhagen	4/18/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -002-(c)-(71)

TITLE OF PROJECT

Role of Cellular Immunity in Pathogenesis of Periodontal Diseases in Humans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. J. E. Horton
Other Investigators: Dr. L. G. Raisz, Dr. J. J. Oppenheim, Dr. S. E. Mergenhagen
Cooperating Units: USA, Inst. of Dental Res. WRAMC, Wash. D. C. School of Medicine
Dept. of Medicine, Univ. of Rochester

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology & Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The role of cellular immunity in periodontal disease is being studied using a variety of in vitro immunoassays. These include lymphocyte transformation by dental plaque material and detection of in vitro production of mediators of cellular immunity. The supernatants of plaque stimulated lymphocyte cultures contain factors that may participate in the destruction of periodontal tissues and bone. Mediators such as cytotoxic lymphotoxin, and an "osteoclast activation factor" which lyses fetal rat bone in vitro are produced and their mechanism of action is being studied.

Total Man Years: 1 1/2
Professional: 1 1/2
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	for J. E. Horton	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. S-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 63 (69)

NIDR-LMI -003-(b)-(69)

TITLE OF PROJECT

Immunological Mechanisms Involved in Histamine Liberation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. William A. Hook
Other Investigators: Dr. S. E. Mergenhagen, Dr. J. J. Oppenheim, Mrs. S. Dougherty
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology & Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The release of histamine and other pharmacologically active substances from mast cells and blood basophiles is being studied. Histamine release is being investigated as one of the immunological effector mechanisms by which antigens, allergens, mitogens or bacterial endotoxins may interact with serum components or with leukocytes to cause inflammation. The interaction of endotoxin with the hamster complement system to generate histamine liberating activity and the stimulation of leukocytes with mitogens to result in histamine release from mast cells is currently under study.

Total Man Years: 2 1/4
Professional: 1 1/4
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William A. Hook	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 62 (69)

NIDR-LMI -004-(b)-(69)

TITLE OF PROJECT

Role of Antibodies and Cellular Interactions in Delayed Hypersensitivity and Lymphocyte Transformation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. J. J. Oppenheim
Other Investigators: Dr. H. Kirchner, Dr. R. Seeger, Miss Linda Weedon & Mr. A. Fridberg
Cooperating Units: George Washington U. Med. School, Dr. H. Brown,
Washington, D. C. Children's Hospital Dr. S. Leikin
NCI Dr. M. Blaese

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology and Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mechanisms by which different cell populations involved in immunological reactions interact are being investigated. The role of thymic dependent T cells and B cells, that produce antibodies, in in vitro lymphoproliferative reactions and in vivo manifestations of delayed hypersensitivity is being studied utilizing agammaglobulinemic chickens (depleted of B cells) and chickens treated with ALS (depleted of T cells). The facility with which macrophage-bound antigens induce delayed hypersensitivity and activate thymic dependent T rather than B types of lymphocytes is also being studied using similar approaches to obtain selected populations of lymphocytes. Antibodies made by B cells have been found to inhibit the lymphoproliferative reactions of T cells in vitro. The role of this apparent feedback control in alleviating symptoms of patients with allergies that are undergoing treatment with hyposensitization is being studied.

Total Man Years: 2 1/2
Professional: 1 1/4
Other: 1 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. J. Oppenheim	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

National Institute of Dental Research

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 62 (69)

NIDR-LMI -005-(b)-(69)

TITLE OF PROJECT

Mechanism of Prolongation of Transplantation of Rat Heart Allografts by Enhancing Antiserum

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. R. Gordon
Other Investigators: Dr. D. Ranney, Dr. J. J. Oppenheim, Mr. Thomas Atchison
Cooperating Units: NHLI, Drs. S. G. Souther and E. B. Stinson
NCI, Dr. M. Mage

NAME AND ADDRESS OF APPLICANT INSTITUTION **Laboratory:** Microbiology & Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Prolongation of heart allografts in rats can be achieved by active immunization which produces antibodies directed against histocompatibility antigen, or by passive transfer of such antisera. Such antisera also specifically suppress in vitro mixed lymphocyte reactions (MLR) involving cells of the allotype with which they react. The nature of responsible serum fraction and mechanism by which the in vitro MLR is inhibited are being studied.

Total Man Years: 1 1/2
Professional: 1 1/4
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	R O Gordon	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publicotian or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 64 (71)

NIDR-IMI -006-(b)-(71)

TITLE OF PROJECT

Isolation, Characterization and Biological Effects of Murine Histocompatibility Antigens from Cells Grown in Continuous Culture

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Jack H. Pincus, Senior Staff Fellow
Other Investigators: Dr. S. I. Chung, Staff Fellow, Dr. Robert Gordon, Dr. David Ranney and Dr. Joost J. Oppenheim
Cooperating Units: Associated Biomedic Systems, Inc., Buffalo, New York

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Immunology
Location: NIDR, NIH, Behtesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The cultured murine leukemia, L1210 containing the H-2^d histocompatibility antigen has been used to isolate a murine histocompatibility antigen. Cells have been evaluated for optimal growth conditions, antigenic constitution and viability during growth. It has been demonstrated that L1210 cultured cells contain approximately twice as much antigen as spleen cells derived from the isogenic DBA/2 mouse. Using a hypertonic salt extraction approximately 10% of the antigen present on the cell surface has been obtained in soluble form. As most of the methods for the solubilization of histocompatibility antigens result in low yields of materials, new methods of extraction are being investigated. These include the use of neutral salts that will disolve lipids without affecting proteins, and low molecular weight cyclic polypeptides. In addition, studies on membranes prepared from L1210 cells are being undertaken to determine the nature of the proteins and the forces holding them together in order to gain further insight into the "ideal" method of extracting histocompatibility antigens.

The biological effects of such soluble histocompatibility antigens are being investigated in in vitro cultures of mouse lymphocytes. These soluble antigens are also administered to allogeneic mice in attempts to modify the in vivo antibody and cell-mediated immunological reactions to transplantation of homografts.

Total Man Years: 2
Professional: 1 1/2
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jack H. Pincus	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

National Institute of Dental Research

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 64 (71)

NIDR-LMI -007-(b)-(71)

TITLE OF PROJECT

Mechanism of Production and Genetic Control of Structurally Restricted Antibodies to Pneumococcal Polysaccharides

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Jack H. Pincus, Sr. Staff Fellow
Other Investigators: None
Cooperating Units: LI/NIAID/NIH
University of Pennsylvania, School of Dental Medicine

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Immunology
~~Location: NIDR, NIH, Bethesda, Maryland 20014~~

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Hyperimmunization of rabbits with either type III or type VIII Pneumococcus results in the production of antibodies specific for the capsular polysaccharide. In a small percentage of these rabbits, antibodies that are structurally restricted are observed. Immunization of close relatives of restricted responders also demonstrates that these rabbits exhibit this trait. A restricted response to these antigens is an heritable trait. By selecting restricted responders and breeding them, two pedigrees of rabbits exhibiting this trait have been established. A characterization of the antibodies produced by such pedigreed animals indicates that they are different with respect to their electrophoretic mobility, allotype, and idiotypic specificity within the pedigrees. The trait is not linked to any known genetic markers.

In order to gain further insight into the mechanism of restricted antibody production, an attempt has been made to produce restricted antihapten antibodies by covalently couping DNP lysine to CNB_r treated pneumococci. Most of the rabbits producing antibodies to this conjugate produced restricted anti DNP antibodies. The antibodies are currently being characterized. A conjugate such as DNP pneumococcus as well as similar hapten bacterial conjugates will be used to probe the immune response.

Total Man Years: 1
Professional: 1/2
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jack H. Pincus	5/3/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -008-(b)-(71)

TITLE OF PROJECT

Chemotactic Factors Produced by Human and Animal Leukocytes and their Role in Mediating Acute and Chronic Inflammatory Reactions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Leonard C. Altman
Other Investigators: Mr. John Kennedy
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The in vivo and in vitro production by leukocytes of factors chemotactic for homologous leukocytes will be studied. These studies will be done in humans and certain animal species will also be investigated. The studies will differentiate between factors chemotactic for granulocytes, monocytes and lymphocytes.

Additionally, the kinetic synthesis of production and characterization of these chemotactic factors will be investigated. Studies will be undertaken to determine which population and/or sub-population of leukocytes is responsible for the production of these chemotactic factors.

And finally, the production of a monocyte chemotactic factor will be correlated with skin test responsiveness and lymphocyte transformation to specific antigens in a normal human population. This correlation will then permit study of human diseases with abnormalities of cell mediated immunity.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Leonard C. Altman M.D.	050372

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -009-(c)-(71)

TITLE OF PROJECT

Correlation of Various In Vitro Bioassays of Tumor Immunity In Man

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Joost J. Oppenheim
Other Investigators: None
Cooperating Units: Dr. R. Herberman, NCI
Dr. J. McCoy, Bionetics

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology & Immunology
Section: Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Study of tumor immunity in man using a number of in vitro bioassays to monitor the effect of tumor and therapy on patients immunological reactivity. These include assays of blastogenic response of patients lymphocytes to tumor cells and solubilized tumor antigens, inhibition of tumor cell growth in vitro and Cr^{51} release by cytotoxically lysed tumor cells.

Total Man Years: 1/4
Professional: 1/4
Other:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joost J Oppenheim	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PHS-166
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National Institute of Dental Research

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 67-(66)

NIDR-LMI -010-(b)-(66)

TITLE OF PROJECT

Phylogenetic Mapping of the Homofermentative Lactic Acid Bacteria

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Jack London, Ph.D.
Other Investigators: Miss Kimberly Kline and Mrs. Sandra Kulczyk
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Microbial Physiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The enzyme, FDP aldolase, from Streptococcus faecalis has been purified and biochemically and physiologically characterized. Following a comparative study of the chemical characteristics of other FDP aldolases found among homofermentative streptococci, lactobacilli and pediococci, the pure enzyme from S. faecalis will be used as an antigen to prepare specific antisera in rabbits. These antisera will then be used to determine whether the respective aldolases are structurally similar. Employing quantitative serological procedures, namely, microcomplement fixation and quantitative precipitin tests, the degree of immunological similarity (which is a direct reflection of the structural similarity) between the various aldolases will be determined. With S. faecalis as a point of reference, the other species of streptococci, as well as species of lactobacilli and pediococci can be fitted into a scheme which will reflect the evolutionary relatedness of the respective organisms.

The relationship between the saprophytic and pathogenic forms of lactic acid bacteria should provide some insight into the course of evolution of the disease producing organisms and their respective invasive mechanisms.

Total Man Years: 2 3/4
Professional: 1
Other: 1 3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jack London	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 66 (61)

NIDR-LMI -011-(b)-(61)

TITLE OF PROJECT

The Purification, Properties, and Regulation of the 6-Phosphogluconate Dehydrogenase from Streptococcus faecalis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Raymond B. Bridges, Ph.D.
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Laboratory of Microbiology & Immunology
Section: Microbial Physiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The 6-phosphogluconate dehydrogenase from Streptococcus faecalis has been purified to homogeneity as demonstrated by disc gel electrophoresis, sedimentation equilibrium, and immunoelectrophoresis. The molecular weight of this enzyme is 108,000 and is composed of two subunits of apparently identical molecular weight. The Michaelis constants for substrate and coenzyme were found to be 2.38×10^{-5}M and 1.46×10^{-5}M, respectively. Fructose-1,6-diphosphate (FDP) has been shown to be a specific inhibitor of this enzyme. FDP is a hyperbolic competitive inhibitor with respect to 6-phosphogluconate and a hyperbolic non-competitive inhibitor with respect to NADP. The K_I for FDP decreases 50-fold by pre-incubation of the negative effector with the enzyme for three minutes. Of the other intermediates of the Embden-Meyerhof and hexose monophosphate pathways, only ribulose-5-phosphate (the product) was shown to inhibit the enzyme. However, ATP and EDTA have been shown to reverse the inhibition observed with FDP, apparently due to the ability of these compounds to complex metal. Kinetics of the inhibition by products have not delineated a mechanism for the order of addition of substrates in the enzyme catalyzed reaction (i.e. if any order exists). Attempts at proving a Schiff base complex between FDP and the enzyme by sodium borohydride reduction were unsuccessful. Sucrose density gradient centrifugation of an enzyme FDP mixture revealed no apparent changes in molecular weight of the enzyme. FDP and 6-phosphogluconate have been shown to be equally effective in protecting the enzyme against inactivation by p-hydroxymercuribenzoate. These data are consistent with the aforementioned kinetic results. However, these data might still be consistent with the hypothesis that FDP is an allosteric negative effector of the 6-phosphogluconate dehydrogenase.

Total Man Years: 1 1/4
Professional: 1
Other: 1/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Raymond B. Bridges	5/3/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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Not for publication or publication reference.

National Institute of Dental Research
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -012-(b)-(72)

TITLE OF PROJECT

Carbohydrate Metabolism and Regulation in Caries Producing Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Joseph E. Ciardi, Ph.D.
Other Investigators: Charles L. Wittenberger, Ph.D.
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology LOCATION: NIDR, NIH, Bethesda, Maryland 20014
Section: Microbial Physiology

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Further studies are underway on the enzyme Dextransucrase from S. mutans to determine the control mechanism responsible for the release of enzyme into growth medium under certain conditions of growth but not under other defined growth conditions with identical carbohydrate source. This enzyme will be further purified and characterized with respect to substrates, activators and especially enzyme inhibitors (Carbohydrate analogs, etc.).

Investigations have also been undertaken to delineate the relationships between extracellular polysaccharide formation, intracellular storage, polysaccharide accumulation, and glycolysis. Several key enzyme activities involved in intracellular polysaccharide and lactate formation are being explored in order to define patterns of metabolic regulation in these organisms.

TOTAL MAN YEARS: 3/4
Professional: 3/4
Other: None

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. E. Ciardi (ctw)	5/4/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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National Institute of Dental Research
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 66 (61)

NIDR-LMI -013-(b)-(61)

TITLE OF PROJECT

Studies on the Regulation of Carbohydrate Metabolism and Lactic Acid Production in Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: C. L. Wittenberger, Ph. D.
Other Investigators: Mrs. M. P. Palumbo
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Microbial Physiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the continuing general purpose of this program to examine fundamental mechanisms by which the biochemical activities of the microbial cell are regulated and, where possible, to delineate the molecular basis for such regulation. These studies are oriented toward explaining physiological phenomena in precise biochemical terms. Specifically, the means by which S. faecalis controls the distribution of glucose carbon between the glycolytic and hexose monophosphate pathways is under investigation. Direct comparative studies have also been made between pathways of carbohydrate catabolism and their regulation in S. faecalis and those operative in S. mutans.

Mannitol and Sorbitol catabolism has been studied in S. mutans and the pathway for the utilization of these hexitols has been delineated. Other studies involving S. mutans, include, 1) the means by which the synthesis of intracellular polysaccharide is regulated and 2) factors which are involved in governing the distribution of "soluble" and cell-associated dextran sucrase.

Total Man Years: 2-3/4
Professional: 1
Other: 1-3/4

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	C. L. Wittenberger	5/3/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 68 (66)

NIDR -LMI -014-(b)-(66)

TITLE OF PROJECT

Systematic Microbiological Taxonomic Studies

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Morrison Rogosa
Other Investigators: Dr. Micah Krichevsky
Cooperating Units: Georgetown Univ., Amer. Type Culture Collection and Bergey's Manual Trust

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section : Microbial Physiology
Location : NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Integrated studies will be continued on common reactions, utilization of substrates and metabolic pathways in the lactic acid bacteria representing chiefly Lactobacillus, Leuconostoc, and Pediococcus. New differential tests and comparative enzyme functions in the lactic acid bacteria will be studied further. Computer storage and information programming of microbial characteristics will continue.

Total Man Years: 2
Professional: 1
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Morrison Rogosa

DATE: May 3, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. 65 (67)

NIDR:-LMI -015-(b)-(67)

TITLE OF PROJECT

Persistent Viral Infections and Virus-Induced Immunopathology

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Abner Louis Notkins, M.D.,Chief, Virology Section, LMI, NIDR
Other Investigators: Akira Niwa, M.D.
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Virology Section
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Certain viruses can induce new antigens on the surface of infected cells. The interaction of immune lymphocytes or antiviral antibody plus complement with these antigens will be investigated. The biochemical events involved in the replication of certain persistent viral infections (e.g., lactic dehydrogenase virus) will be studied.

Total Man Years: 2-1/4
Professional: 1-1/4
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Abner Louis Notkins, MD	May 3, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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Not for publication or publication reference.

National Institute of Dental Research
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -016-(b)-(71)

TITLE OF PROJECT

Detection of Viral Antigens and Antiviral Antibody

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Abner Louis Notkins, M.D., Chief, Virology Section, LMI, NIDR
Other Investigators: Kozaburo Hayashi and Joel Rosenthal
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Virology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Efforts will be made to develop sensitive and rapid methods for detecting viral antigens and antiviral antibody by use of radioimmunoassays. These and other methods then will be used to study the role of antiviral antibody in the pathogenesis of persistent viral infections and autoimmune diseases.

Total Man Years: 3-1/4
Professional: 1-1/4
Other: 2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Abner Louis Notkins, MD	May 3, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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National Institute of Dental Research
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR LMI -017-(b)-(70)

TITLE OF PROJECT

Cellular Immunity and Viral Infections

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Abner Louis Notkins, M.D.
Other Investigators: Gary Rosenberg, Don Lodmell and Charles Wohlenberg
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Laboratory: Microbiology and Immunology
Section: Virology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Efforts will be made to study the cellular immune response to viral infections by use of in vitro models. The role of lymphocytes, macrophages and biological mediators will be investigated.

Total Man Years: 4-1/4
Professional: 2-1/4
Other: 2

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Abner Louis Notkins, MD	May 3, 1972

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-LMI -018-(b)-(71)

TITLE OF PROJECT

Diabetes in Mice as a Model System for Viral Induced Endocrine Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Abner Louis Notkins, M.D., Chief, Virology Section, LMI, NIDR

Other Investigators: D. Wark Boucher, Ph. D.

Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Virology
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The possibility of a virus as an etiologic agent in diabetes mellitus will be investigated using mice as a model system. In the study two viruses will be used, the M strain of encephalomyocarditis virus and coxsackie virus B4. Studies with Coxsackie B4 will initially involve determining if infection in mice does cause diabetes as measured by appearance of abnormal glucose and insulin levels. Subsequent studies will be concerned with the mechanism by which diabetes is produced.

Total Man Years: 2-1/4
Professional: 1-1/4
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Abner Louis Notkins, M.D.	May 3, 1972

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -001(c)-(72)

TITLE OF PROJECT

Effect of Paraviruses on the Jaws, Teeth and Periodontium of the Hamster

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Paul N. Baer, D.D.S., Dental Director
Other Investigators: None
Cooperating Units: Lawrence Kilham, M.D., Dartmouth Medical School

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It has been shown that the various paraviruses, the RV, H-1, and MVM, affect the development of the skull, produce deformities of the teeth, increase the amount and severity of alveolar bone destruction and produce odontogenic growths, cementomas and odontomas.

Total Man Years: 1 1/2
Professional: 1/2
Other: 1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Paul N. Baer	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-95(c)-(70)

NIDR-OMS -002(c)-(70)

TITLE OF PROJECT

Hemodynamics of Oral-Facial Tissues

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Richard L. Christiansen, Dental Director
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A system was previously developed to control blood perfusion to the mandible and mandibular teeth. The mandibular artery and vein were isolated and cannulated on 8 dogs. The influence of various drugs on hemodynamic parameters was monitored. It was found that catecholamines and serotonin produced a 25% increase in vascular resistance to mandibular blood flow while histamine decreased resistance by 15%. The data produced a curvillinear relationship between perfused flow and arteriovenous pressure difference with the convexity toward the pressure axis. This relationship is consistent with reports from studies of nonosseousvascular beds.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Christiansen	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-94(c)-(65)

NIDR-OMS -003-(c)-(65)

TITLE OF PROJECT

Study of Oral Area Motor Mechanisms by Use of Displacement and Pressure Transducers

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Dr. Richard L. Christiansen, Dental Director
Other Investigators: None
Cooperating Units: Instrument Fabrication Division, NIH.
Dr. K. Moller, School of Dentistry, University of Minnesota.
School of Dentistry, Georgetown University

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Certain groups of patients, such as cleft palate, exhibit varying degrees of articulation errors and an overall perceptable hypernasality. Velar motion was instantaneously monitored via a displacement transducer; the transducer output also provided a visual feed-back to assist in modification of velar movement by increased elevation and increased velopharyngeal closure. Increased elevation was produced during conditioning sessions and during post-conditioning speech.

In the area of intraoral pressure measurement of seven subjects lateral pressure of the relaxed tongue was monitored with sensitive pressure transducers. The relaxed pressure was found to be of low magnitude (< 0.5 g/mm^2).

Total Man Years: 1/2
Professional: 1/2
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Christiansen	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -004-(c)-(72)

TITLE OF PROJECT

Effect of Anti-serotonin and Anti-histamine Agents on the Immune Complex Disease of NZB/W F_1 Hybrid Mice

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Thomas M. Chused, Sr. Staff Fellow
Other Investigators: Thomas M. Tarpley, Jr., Sr. Dental Surgeon, EP, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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It has been shown that the combination of anti-histamine and anti-serotonin can nearly prevent the immune complex nephritis associated with acute serum sickness in rabbits. New Zealand Black/White F_1 hybrid mice develop immune-complex nephritis much like human systemic lupus erythematosus. We are investigating the effect of histamine and serotonin antagonists in these mice.

Total Man Years: 17/24
Professional: 3/8
Other: 1/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	T. Thomas M. Chused, M.D.	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -005-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Functional Capacity of Thymus Derived Cells in New Zealand Mice

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Thomas M. Chused, Sr. Staff Fellow
Other Investigators: John A. Hardin, Surgeon, Oral Medicine and Surgery
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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It has been noted that 6-month old New Zealand mice have a decreased capacity to reject skin grafts. We are investigating the functional capacity of their thymus-derived (T) cells by in vivo graft versus host reaction, and in vitro response to phytohemaglutinin, conconavalin and allogeneic lymphocytes, as well as sensitivity to anti- and anti-immunoglobulin antibodies. We wish to determine the life span, migratory behavior and antigenic properties of the deficient population.

Total Man Years: 17/24
Professional: 3/8
Other: 1/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Chused, M.D.	5/17/72

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METHOD OF SUPPORT *(Check one)*

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -006-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Effect of Antithymocyte Serum on the Response to Poly I·Poly C in Normal and New Zealand Mice

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Thomas M. Chused, Sr. Staff Fellow
Other Investigators: None
Cooperating Units: Alfred D. Steinberg, A&R, NIAMD

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Antithymocyte serum (ATS) increases the immune response to SRBC in most strains of mice. We have observed the same effect with poly I·poly C (rI·rC), but it is considerably diminished in NZB/W F_1 hybrids. We are now investigating the cell type involved and the affect of various ATS-rI·rC regimens.

Total Man Years: 17/24
Professional: 3/8
Other: 1/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Chused M.D.	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -007-(c)-68

Prev. Ser. No. NIDR-97-(c)-(68)

TITLE OF PROJECT

Mechanisms of Cryoprecipitation in Cryoglobulins

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Norman A. Cummings, Medical Officer
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mechanisms to explain cold insolubility in cryoglobulins are explored by immunochemical and physicochemical techniques. Peptide mapping of appropriate (CRYO) gamma globulin fragments will be emphasized in terms of chromatographic behavior and amino acid content.

Total Man Years: 7/12
Professional: 1/4
Other: 1/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings, MD	5/17/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -008-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Immunochemical Studies of Sjögren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Norman A. Cummings, Medical Officer
Other Investigators: John Hardin, Surgeon
Thomas M. Chused, Sr. Staff Fellow
Thomas M. Tarpley, Jr., Dental Surgeon, EP, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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The immunochemical aspects of salivary gland antigens will be assessed in Sjögren's syndrome. Ability to inhibit anti-salivary gland antibody in fluorescence or autoradiographic techniques will be used to identify the antigens isolated from the gland by column chromatography. Protein fractions from the gland will also be evaluated for their ability to stimulate transformation of lymphocytes from patients.

Total Man Years: 23/24
Professional: 5/8
Other: 1/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings MD	5/17/72

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METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-96-(c)-(68)

NIDR-OMS -009-(c)-(68)

TITLE OF PROJECT

Study of Behcet's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Norman A. Cummings, Medical Officer
Other Investigators: John A. Hardin, Surgeon
Bradley R. Thach, Clinical Associate, Oral Pharyngeal Development
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Patients with Behcet's syndrome will be studied with regard to the natural history of their clinical course. Their immunologic response to various antigens, the incidence and extent of neurologic involvement, and the response to various therapeutic modalities will also be assessed.

Total Man Years: 7/8
Professional: 7/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Norman A. Cummings MD	5/17/72

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METHOD OF SUPPORT *(Check one)*

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FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-104-(c)-(70)

NIDR-OMS -010-(c)-(70)

TITLE OF PROJECT

Evaluation of Dental Implants

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: George E. Garrington, D.D.S.
Other Investigators: Patrick Looney, D.D.S.
Cooperating Units: Philip M. Lightbody, D.D.S., Winter Park, Florida

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Porous ceramic or metallic implants are being investigated in New Zealand white rabbits and Rhesus monkeys. Materials used include calcium aluminate, aluminum oxide and titanium. Controlled porosities from 50 to 200 microns as well as some specimens with random gross porosity are used. Thirty-five implants have been placed (16 in rabbits, 19 in monkeys). In the rabbits all implants are ceramic; 6 are subcutaneous or intramuscular; 8 are in cavities prepared in the femur; and 2 are in cavities prepared in the mandibular ramus. Ten implants in monkeys are precise ceramic duplicates of freshly extracted teeth implanted in the extraction site; five are precise ceramic duplicates of the root only; and four are porous titanium cylinders placed in fresh extraction sites. All procedures have been well tolerated by the animals. Implants have now been in place for periods up to 2 years. The study is designed to elicit information regarding tissue compatibility, attachment mechanisms, periodontal and alveolar reaction, and functional performance. Present intention is to perform more implants with design and technique variations for ultimate overall appraisal of the feasibility of dental implantation.

Total Man Years: 1
Professional: 1/2
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Geo. E. Garrington	May 17, 1972

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METHOD OF SUPPORT *(Check one)*

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Serial No. None

NIDR-OMS -011-(c)-(72)

TITLE OF PROJECT

Allogenic Tooth Transplantation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Edward A. Graykowski, D.D.S., M.D.
Other Investigators: Samuel Kakehashi, D.D.S.
Thomas Chused, M.D.
John Folio, D.D.S.
Patrick Looney, D.D.S.
Jack Pincus,
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK — *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The feasibility of allogenic tooth transplantation from donor to recipient that have been matched with respect to their histo-compatibility and ABO blood group antigens is being explored. The function, survival, and usefulness of such teeth will be evaluated with long term follow-up.

Total Man Years: 3 3/4
Professional: 1 1/4
Other: 2 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward A. Graykowski	May 17, 1972

DO NOT WRITE BELOW THIS LINE — FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.- None

NIDR-OMS -012-(c)-(72)

TITLE OF PROJECT

Relationship of lymphocyte antigens in familial aphthous stomatitis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Edward A. Graykowski, M.D., D.D.S.
Other Investigators: Thomas M. Chused, M.D.
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The relationship of familial incidence in recurrent aphthous stomatitis to histocompatible lymphocyte antigen is being investigated by determining HLA and ABO blood group antigens in aphthous family groups.

Total Man Years: 7/8
Professional: 3/8
Other: 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward A. Graykowski	May 17, 1972

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -013-(c)-(72)

TITLE OF PROJECT

GVH* Reactions in NZB/w Mice.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: John A. Hardin, M.D.
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Oral Medicine and Surgery
NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

GVH reactions in NZB/w mice. The ability of spleen cells from old NZB/w mice has been shown to be deficient in producing a GVH reaction. We are currently attempting to determine which of the various lymphocyte cell populations might be defective in the older NZB/w mouse thus resulting in an impaired GVH reaction when these cells are injected into newborn recipients.

*Graft-versus-host

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John A. Hardin M.D.	5/5/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publicat on reference.

Prev. Ser. No. None

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -014 (c) (72)

TITLE OF PROJECT

Sjögren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: John A. Hardin, M.D., Surgeon
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Patients with Sjögren's Syndrome are admitted for evaluation. We are gathering clinical data for this patient population. Efforts are also being made to isolate salivary gland antigen to which lymphocytes from these patients will respond.

Total Man Years: 1/4
Professional: 1/4
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John A. Hardin, M.D.	5/5/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -015-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Tissue Factor Production By Lymphocytes

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: John A. Hardin, M.D.
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

When grown in tissue culture lymphocytes produce a procoagulant which has been characterized as tissue factor. Current investigations are aimed at determining the biological significance of this in inflammation and coagulation.

Total Man Years: 1/8
Professional: 1/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John A. Hardin, M.D.	May 17, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -016-(c)-(72)

TITLE OF PROJECT

Development of an Image Preprocessing Dental Radiographic System

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Richard L. Webber, Senior Dental Surgeon
Other Investigators: None
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A new type of radiographic system is to be built which couples an intraoral source of radiation to an extraoral transducer. The output of the device is an immediate display which can be stored both photographically and electronically. The latter capability also permits the output to be preprocessed in ways which have been demonstrated to assist in the detection of caries. The design provides for the production of images using a theoretical minimum of exposure to ionizing radiation.

Total Man Years: 1/2
Professional: 1/2
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Webber	May 17, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

Prev. Ser. No. None

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -017-(c)-(72)

TITLE OF PROJECT

Selection and Clinical Testing of Techniques for Preprocessing Visual Images Containing Diagnostic Information.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Richard L. Webber, Senior Dental Surgeon, Oral Medicine & Surgery, NIDR
Other Investigators: John Folio, Senior Dental Surgeon, Dental Services Branch, NIDR
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Research is being directed toward the selection and testing of heuristics designed to restrict the domain of promising transformations available for manipulating the display of diagnostic information. Related studies are underway which demonstrate the degree to which selected preprocessing techniques improve diagnostic performance obtainable in various clinical situations. Transformations of particular interest are currently being related to the interpretation of radiographs.

Total Man Years: 5/8
Professional: 5/8
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Webber	May 17, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -018-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Sjögren's Syndrome Saliva

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator: Robert O. Wolf, D.D.S., Dental Director
Other Investigators: Steven M. Herzberg, M.D., Clinical Associate
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Using the NIH Sjögren's Syndrome population we are investigating the disc acrylamide electrophoretic protein patterns, cytology and flow rates of the parotid saliva. The values are being compared to non-Sjögren's Syndrome values. More evidence concerning the etiology of this disorder is expected to result from this project.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	ROBERT O. WOLF DDS.	May 17, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -019-(c)-(72)

Prev. Ser. No. None

TITLE OF PROJECT

Salivary Gland Studies

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Robert O. Wolf, D.D.S., Dental Director
Other Investigators: Steven M. Herzberg, M.D., Clinical Associate
Cooperating Units: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The study of salivary isoamylases of human tissues indicates that at least one of the components is probably under detectable gene control. Definitive family studies are planned. Human amniotic fluid and human pleural fluid isoamylases are being investigated for possible diagnostic value. Salivary gland disease is being studied by sequential salivary scintigraphy siolography, parotid flow rate, dytology and saliva analysis.

Total Man Years: 1
Professional: 1
Other: 0

PROFESSIONAL SCHODL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	ROBERT O WOLF, DDS.	May 17, 1972

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -020-(c)-(72)

TITLE OF PROJECT

Symposia on Oral Sensation and Perception

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: James F. Bosma
Other Investigators: None
Cooperating Units: Fogarty International Center

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Med. & Surg.
Section: Oral & Pharyngeal Development
~~Location: NIH, Bethesda, Maryland 20014~~

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The Third Symposium on Oral Sensation and Perception: The Mouth of the Infant, was held under joint NIDR-Fogarty International Center sponsorship November 23-25, 1970. This will be in print by Thomas: Publisher, in Summer of 1972. This reports a conference held November 23-25, 1970. Its 18 Chapters are concerned with anatomy of the oral area, sensory receptors, infant oral functions, and studies of infants abnormal in form and/or function.

Total Man Years: 1
Professional: 1/3
Other: 2/3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James F. Bosma	5/17/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

NIDR-OMS -021-(c)-(72)

Prev. Ser. No. None

PRIOR SER. NO.

TITLE OF PROJECT

Microscopic Anatomy of the Fetal and Newborn Human Lip

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Bradley T. Thach
Other Investigators: James F. Bosma
Cooperating Units: M.A. Larsen

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Med. & Surg.
Section: Oral & Pharyngeal Development
Location: NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Tissue specimens from 15-20 human fetuses and newborns will be obtained in cooperation with Department of Pathology in local hospitals. The histology of the transitional zone of the lip will be described using standard light microscope techniques. Suitable specimens will be examined by electron microscopy from time to time. Sections for nerve stains and histochemistry will also be made.

Total Man Years: 2
Professional: 1 1/12
Other: 11/12

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Bradley T. Thach	5/17/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

NIDR-OMS -022 (c) (72)

TITLE OF PROJECT

Anatomical Studies of Head and Fetus at Term

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: James F. Bosma, M.D., Chief, Oral Pharyngeal Development Section, NIDR
Other Investigators: Beverly Etter, Illustrator, Oral Pharyngeal Development Section, NIDR
Cooperating Units: Robert Pierce, Clinical Center, NIH; St. Joseph's Mercy Hospital, Rockford, Illinois
Michael Mainen, M.D., USPHS Hospital, Baltimore, Maryland
Howard Bartner, Chief, Medical Illustrations Section, MAPB, NIH
Keiko Moore, Medical Illustrator, Washington, D.C.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Branch: Oral Medicine and Surgery
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This is the third year of gross anatomical studies of the face, pharynx and cranium of the human fetus at term. Successive dissections with 32 corresponding illustrations of the head have been completed. Also 9 coronal cross-section illustrations. A portion of these dissection illustrations were included in a brief anatomical description for the Third Symposium on Oral Sensation and Perception: The Mouth of the Infant, now in press.

Representative matching crania have been illustrated in general views, in coronal and in transverse sections. Each of the anatomical sections matches a tomoradiograph. This material is now in final stage of preparation as an Atlas of Cranial Anatomical Sections and Tomoradiographs of the Human Fetus at Term, authored by Robert Pierce (former Associate in Radiology at the Clinical Center), Michael Mainen (former Clinical Associate in this Section), and James Bosma.

In an additional study of the fetal cranium, illustrations of selected areas of crania and individual bones are in preparation. These, supplemented by fractions of the section illustrations noted above and a small number of radiographs and detail photographs, comprise the material of a prospective general book, the Head Skeleton of the Human Fetus at Term, by J. Bosma.

Total Man Years: 2 1/3
Professional: 5/6
Other: 1 1/2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. Bosma	May 17, 1972

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NIDR ANNUAL REPORT - FY 72

RESEARCH CONTRACTS AND INDEXES

NIDR ANNUAL REPORT - FY 72

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RESEARCH CONTRACTS BY NUMBER

* Report year for Contracts: 4/1/71 through 3/31/72

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RESEARCH CONTRACTS BY PARTY/AGENCY

* Report year for Contracts: 4/1/71 through 3/31/72

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RESEARCH CONTRACTS BY PROJECT DIRECTOR

* Report year for Contracts: 4/1/71 through 3/31/72

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RESEARCH CONTRACTS BY PROJECT OFFICER

* Report year for Contracts: 4/1/71 through 3/31/72

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

P.L. 480 AND INTERAGENCY AGREEMENT RESEARCH SUPPLEMENTAL INFORMATION RECORD

CHECK ONE:
☐ P.L. 480 Agreement ☒ Interagency Agreement
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I - FILL IN THIS INFORMATION AND ATTACH A FACE PAGE FROM AGREEMENT WITH EVERY SUBMITTAL

NAME OF OTHER PARTY/AGENCY TO AGREEMENT

U. S. Coast Guard
Governors Island, New York

AGREEMENT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIDR-01	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* List One
	☐ AD HOC COMMITTEE ☐ OTHER ☐ STANDING COMMITTEE	Dr. Harold R. Englander

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

	NO. OF YEARS	DOLLAR LEVEL OF SUPPORT FOR EACH
NIH COMMITMENT	one	$ 36,400

SUMMARY OF AGREEMENT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW AGREEMENT: A Xerox copy of the work scope defined within the agreement is permissible; if 100 words or less.
FOR RENEWAL AGREEMENT OR CHANGES: Complete only if changed from prior agreement period.

The population on Governors Island has been used to conduct the following projects:

1. The effect of frequently repeated fluoride toplications on caries in the deciduous dentition

2. Epidemiologic studies on the occurrence and distribution of cariogenic streptococci

3. Studies on adhesive sealants

4. Prevalence of root surface caries in adults

TITLE OF AGREEMENT, IF ANY

"Anticaries Effect of Repeated 27,000 Topical Fluoride Treatments on the Deciduous Dentition"

DISCIPLINE, SPECIALTY, FIELD *(DRG Code)*	PERIOD OF AGREEMENT *(Dates From - To)*	DATE AGREEMENT SIGNED BY NIH	ADDRESS OF OTHER PARTY/AGENCY

INVESTIGATOR INFORMATION (Complete for new agreements or for subsequent changes - otherwise leave blank):

	NAME *(Last, First, Middle Initial)*	DEGREES HELD	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week- in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Capt. E. D. Woolridge	D.D.S.		5
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Cdr. G. T. Ward	D.D.S.		8
	2. Dr. H. M. Stiles	D.D.S.,Ph.D.		16
	3.			

NIH-1688-2
12-70

*FIC/OFM will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

P.L. 480 AND INTERAGENCY AGREEMENT RESEARCH SUPPLEMENTAL INFORMATION RECORD

CHECK ONE:
☐ P.L. 480 Agreement ☒ Interagency Agreement
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I - FILL IN THIS INFORMATION AND ATTACH A FACE PAGE FROM AGREEMENT WITH EVERY SUBMITTAL

NAME OF OTHER PARTY AGENCY TO AGREEMENT

National Bureau of Standards

AGREEMENT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIDR--02	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* List One
	☐ AD HOC COMMITTEE ☐ OTHER ☐ STANDING COMMITTEE	Dr. Richard C. Greulich

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

	NO. OF YEARS	DOLLAR LEVEL OF SUPPORT FOR EACH
NIH COMMITMENT	one	$ 263,000

SUMMARY OF AGREEMENT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW AGREEMENT: A Xerox copy of the work scope defined within the agreement is permissible; if 100 words or less.
FOR RENEWAL AGREEMENT OR CHANGES: Complete only if changed from prior agreement period.

TITLE OF AGREEMENT, IF ANY

"Characterization of the Tooth"

DISCIPLINE, SPECIALTY, FIELD *(DRG Code)*	PERIOD OF AGREEMENT *(Dates From - To)*	DATE AGREEMENT SIGNED BY NIH	ADDRESS OF OTHER PARTY/AGENCY
	7/1/71 - 6/30/72	9/22/71	Washington, D. C.

INVESTIGATOR INFORMATION (Complete for new agreements or for subsequent changes - otherwise leave blank):

	NAME *(Last, First, Middle Initial)*	DEGREES HELD	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week- in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. James N. Cassel		176-09-5667	12
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. George Dickson		317-03-9258	40
	2. Gerhard M. Brauer		578-58-9834	18
	3.			

NIH-1688-2
12-70

*FIC/OFM will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

P.L. 480 AND INTERAGENCY AGREEMENT RESEARCH SUPPLEMENTAL INFORMATION RECORD

CHECK ONE:
☐ P.L. 480 Agreement ☐ Interagency Agreement
☒ New ☐ Terminal
☐ Renewal ☐ Change

SECTION I - FILL IN THIS INFORMATION AND ATTACH A FACE PAGE FROM AGREEMENT WITH EVERY SUBMITTAL

NAME OF OTHER PARTY/AGENCY TO AGREEMENT

Indian Health Service, HSMHA
HEW, Rockville, Maryland 20852

AGREEMENT NUMBER *(Include Supplemental Agreement No., if any.)*	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIDR - 05	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* List One
5/25/71	☐ AD HOC COMMITTEE ☐ OTHER ☒ STANDING COMMITTEE	Dr. L. Ariel Thomson

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

NIH COMMITMENT	NO. OF YEARS	DOLLAR LEVEL OF SUPPORT FOR EACH
	one	$ 26,249.18

SUMMARY OF AGREEMENT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW AGREEMENT: A Xerox copy of the work scope defined within the agreement is permissible; if 100 words or less.
FOR RENEWAL AGREEMENT OR CHANGES: Complete only if changed from prior agreement period.

Purpose of Project is to determine the dental caries preventive benefit of a combined program of tooth sealant and repeated fluoride application.

Two groups of American Indian 5th and 6th graders will be randomly assigned to receive maintenance care or preventive measures with maintenance care. Both groups will have all accumulated carious lesions restored before the study commences and receive additional care as required. The Public Health significance of the preventive measures will be determined by contrasting the care required during a three year observation period to estimate the cost benefit.

TITLE OF AGREEMENT, IF ANY

"Clinical Control of Smooth Surface and Pit and Fissure Caries"

DISCIPLINE, SPECIALTY, FIELD *(DRG Code)*	PERIOD OF AGREEMENT *(Dates From - To)*	DATE AGREEMENT SIGNED BY NIH	ADDRESS OF OTHER PARTY/AGENCY
	10/1/71 - 9/30/72	10/1/71	

INVESTIGATOR INFORMATION (Complete for new agreements or for subsequent changes - otherwise leave blank):

	NAME *(Last, First, Middle Initial)*	DEGREES HELD	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week - in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. John Butts	D.D.S.,MPH		3
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Douglas Smoli	D.D.S.		12
	2.			
	3.			

NIH-1688-2
12-70

*FIC/OFM will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminol
☐ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Naval Dental Research Institute
Great Lakes, Illinois

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIDR - 06	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
	☐ AD HOC COMMITTEE ☐ STANDING COMMITTEE	Dr. Harold Englander

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* $17,999

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

To provide the personnel, equipment, and expendable supplies to provide analytical procedures per year principally to provide accurate quantification of calcium and fluoride in tooth enamel samples.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Captain Harris J. Keene		
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

P.L. 480 AND INTERAGENCY AGREEMENT RESEARCH SUPPLEMENTAL INFORMATION RECORD

CHECK ONE:
☐ P.L. 480 Agreement ☒ Interagency Agreement

☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I - FILL IN THIS INFORMATION AND ATTACH A FACE PAGE FROM AGREEMENT WITH EVERY SUBMITTAL

NAME OF OTHER PARTY/AGENCY TO AGREEMENT

Division of Dental Health, BHME, -- San Francisco
National Institutes of Health

AGREEMENT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIDR-08	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* List One
	☒ AD HOC COMMITTEE ☐ OTHER ☐ STANDING COMMITTEE	Dr. Robert J. McCune

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

	NO. OF YEARS	DOLLAR LEVEL OF SUPPORT FOR EACH
NIH COMMITMENT	One	$ 9,000

SUMMARY OF AGREEMENT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW AGREEMENT: A Xerox copy of the work scope defined within the agreement is permissible; if 100 words or less.
FOR RENEWAL AGREEMENT OR CHANGES: Complete only if changed from prior agreement period.

Scope of services includes data processing and statistical services beginning with preparation of examination forms through the selection and preparation os statistical tables to be used in a publication, statistical testing of results, and preparation of written statistical interpretation of findings.

a. Study of four sealants initiated in Maracaibo, Venezuela in April, 1970.
b. Study of four sealants utilizing a half-mouth design, initiated in October, 1970.
c. Study of one sealant in a high fluoride area initiated in September, 1970.
d. Study of several sealants initiated in February, 1972.

TITLE OF AGREEMENT, IF ANY

"Obtaining Data Processing and Statistical Analysis Services on Sealants"

DISCIPLINE, SPECIALTY, FIELD *(DRG Code)*	PERIOD OF AGREEMENT *(Dates From - To)*	DATE AGREEMENT SIGNED BY NIH	ADDRESS OF OTHER PARTY/AGENCY
	10/20/71 - 6/30/72	10/20/72	

INVESTIGATOR INFORMATION (Complete for new agreements or for subsequent changes - otherwise leave blank):

	NAME *(Last, First, Middle Initial)*	DEGREES HELD	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week- in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	John F. Cvar	A.B.	554-346-300	20
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.			
	2.			
	3.			

NIH-1688-2
12-70

*FIC/OFM will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Southwest Foundation for Research and Education
7480 West Commerce St.
San Antonio, Texas 78228

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
PH-43-67-1475, S. A. #6	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
3/10/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. James E. Hamner, III

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The main objective of this study is to produce carcinoma in the baboon's cheek pouch, with a secondary objective of studying the carcinogenic potential of each of the ingredients of betel quid, namely: betel leaf, areca nut, lime, and tobacco, and also to study their interplay. The baboons are divided into two groups i.e., plain betel quid and betel quid plus tobacco. They are maintained on a protein deficient diet. Cheek pouches are created surgically, and the betel quid inserted three times per week.

Note: This is a long term study and the current year effort will parallel closely the research done over the past 3 years.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr, O. M. Reed		2
OTHER SENIOR SCIENTISTS (Limit to 3)	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminol
☒ Renewol ☐ Chonge

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Southwest Foundation for Research and Education
7480 W. Commerce Street
San Antonio, Texas 78228

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
PH 43-67-1476, S. A. #6	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
3/29/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. J. E. Hamner, III

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The objectives of this research effort are to observe in time sequence the response of the surrounding periodontium to the implantation of ceramic, polymethylmethacrylate, prolyte carbons, titanium, and other possible artificial materials and to the heterogenous transplantation of natural teeth in adult baboons.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. O. M. Reed		3
OTHER SENIOR SCIENTISTS (Limit to 3)	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS SUPPLEMENTAL INFORMATION RECORD

CHECK ONE

☐ New ☐ Terminal

☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: University of Tennessee
Memphis, Tennessee

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
PH 43-68-1315	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
4/24/70	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. James E. Hamner, III

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Independently and not as an agent of the Government, the Contractor will exert its best efforts to develop standardized toxicity testing procedures for dental materials. Specifically, the Contractor will:

1. Develop an initial testing protocol for dental materials and products.

2. Develop a scoring system which may be helpful in delineating the degree of toxicity.

3. Perform toxicity tests on selected candidate materials and products.

Note: The workscope did not change during this renewal period, however since the contract workscope has never been furnished previously, we are including it above for information purposes.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. John Autian		as required
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. James Turner		as required
	2. Dr. Homer Lawrence		6
	3. Dr. Elwood Dillingham		4

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
The Kendall Company
Barrington, Ill.

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
PH-43-69-1262	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
5/15/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Harold R. Englander

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Fluoride (F), calcium, phosphate and other analyses on the outer layers of enamel of exfoliated deciduous, extracted permanent teeth and other substances are performed in field studies with various F compounds and formulations conducted by NIDR and others.

F analysis is also performed on enamel biopsy specimens. Studies are conducted on the acquisition of F by extracted teeth soaked in various F compounds; and on methods to improve F uptake in teeth in vivo. The enamel biopsy technic is tested and refined. New research leads are developed and initiated on F research in human beings and animals.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Mr. James R. Mellberg		24
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminol
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Temple University of the Commonwealth System of Higher Education
Broad Street and Montgomery Avenue
Philadelphia, Pennsylvania 19122

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH 69-2066	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
4/13/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Charles J. Donnelly

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

A clinical and radiographic description of root caries lesions will be made and criteria established for differential diagnosis. An examination procedure will be developed together with a scoring system suitable for epidemiological and clinical studies.

The contractor will use the procedure in examining several hundred subjects for evidence of root caries. Data will be recorded in a systematic fashion and submitted to the Government for analysis.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. Richard D. Mumma, Jr., D.D.S., M.P.H.	104-28-7582	8
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. Neal W. Chilton, D.D.S., M.P.H.	125-10-4385	8
	2. Dr. Stanley P. Hazen, D.D.S., M.S.		8
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
Stanford Research Institute
Menlo Park, California 94025

CONTRACT NUMBER *(Include Supplemental Agreement No., if any.)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-69-2223 6/26/70 - 11/25/71	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
11/11/70	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Anthony A. Rizzo

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* $51,824

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The research in this contract consists of two phases: 1. synthesis of organic polyphosphonates and 2. examination of the polymers as constituents of tooth cavity restoration materials.
The contractor will: 1. synthesize 2 types of phosphonated polymers, one with phosphonic acid groups as the only polar substituent and one with other functional groups in addition to accomplish binding to a second polymeric solid phase. 2. Evaluate polyphosphonates as a basis for restoration material in 2 phases: (a) adaptation to the cavity wall and (b) mechanical properties of the new materials.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Michael Anbar		1/12th of time
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Sr. Professional (unnamed)		1/4 of time
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
Stickney Township Health Dept.
Stickney, Illinois

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-70-2135	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
	[ ] AD HOC COMMITTEE [ ] STANDING COMMITTEE	Dr. Harold R. Englander

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

To determine whether children in a fluoridated area will show significant anti-caries benefits after the outer 5 microns of enamel of their teeth have acquired at least 3,000 ppm fluoride. Treatment involves 25 consecutive, 15 minute topical NaF applications by mouthpiece of a gel containing 1.23 percent F.

To assess the level of fluoride acquisition and retention by the enamel from the topical treatments.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Gene Franchi		
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

Battelle Memorial Institute
Columbus, Ohio

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**		INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH 70-2237	6/26/70-6/25/72	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
5/4/71	☒ AD HOC COMMITTEE ☐ STANDING COMMITTEE	Dr. Robert J. McCune

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 3,750

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The research is directed toward determining the chemical and physical properties of mussel cement, both hardened and unhardened, with the ultimate goal of synthesizing it. Representatives of two species of mussels, M. edulis and M. californianus, will be used. Histochemical identification of the specific secretory glands and all cells and tissues contributing to the formation of the adhesive, as well as the biochemical requirements for the formation of the cement, will be made. Work will continue on purifying and characterizing the enzyme polyphenol oxidase. Since the principal component of the adhesive is a protein, major effort will be expended in its characterization.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Robert E. Hillman	131-26-6414	6
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Robert H. Engel	128-28-5954	6
	2. Dr. Carl W. Melton		6
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

The Franklin Institute of the State of Pennsylvania

CONTRACT NUMBER *Include Supplemental Agreement No., if any)**		INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH 70-2238	6/25/71-6/25/72	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
5/4/71	☒ AD HOC COMMITTEE ☐ STANDING COMMITTEE	Dr. Anthony Rizzo

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 5,056

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The contractor will establish and/or maintain a mussel colony and other organisms as required by the study.

Initial studies will be directed toward identifying the specific locality of secretory glands, specific secretory glands, specific secretory cells and identification of biochemical requirements for cementum synthesis. Dissection will be directed toward the collection of cement and/or cement components prior to secretion.

Using such analytical methods as may be appropriate, the cement and/or its components will be chemically and physicably identified before secretion, immediately after secretion and after aged cement has been attached for periods of time.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes • otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	E. Thelan		4
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. P. S. Francis		1
	2. H. J. Bowen		16
	3. Mitchell		19

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Forsyth Dental Center
Boston, Massachusetts

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-70-2244	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
4/23/70	☒ AD HOC COMMITTEE ☐ STANDING COMMITTEE	Dr. Harold R. Englander

SECTION II – FOR NEW, RENEW CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

To determine whether differences in dental caries experience in groups of adolescents, native to communities with either 1ppm F or above in the water supplies or with fluoride-deficient waters, are related to concentrations of fluoride in the outermost surface of the enamel of permanent teeth.

To determine whether the differences in caries experience and any differences in enamel fluoride concentrations are associated with traces of aluminum, molybdenum, titanium, copper, ziconium and other trace elements in the water supplies.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Finn Brudevold		2
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: American Speech and Hearing Association
Washington, D. C.

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-643	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
12/70	[X] AD HOC COMMITTEE [ ] STANDING COMMITTEE	Dr. Zora J. Griffo

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The contractor shall conduct a conference entitled "Cleft Palate Research -- The State of the Art" which shall be designed to assess the achievements, directions, and needs of the several disciplines which deal directly with the pathology of cleft lip and palate.

Specifically, the contractor shall: (1) Assemble a small interdisciplinary planning committee which shall, in cooperation with the Project Officer, develp plans for the meeting and select participants; (2) Conduct the conference at a location acceptable to the Project Officer; (3) Compile and edit the proceedings in final form suitable for publication, and submit to the Project Officer.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Kenneth O. Johnson	Unknown	6 hrs/wk
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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☐ New ☐ Terminal
☒ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: University of Miami

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2013	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
7/27/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. James P. Carlos

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor shall provide the necessary staff, facilities and populations to conduct clinical studies of potential anti-caries agents encompassing the following objectives:

1. To test the hypothesis that certain strains of dextran-forming streptococci are etiologically involved in the induction of human dental caries.

2. To study the feasibility of the use of the enzyme, dextranase, as an anti-plaque and caries-inhibitory agent in humans.

3. To study the effect of long-term use of dextranase on the oral streptococcal flora.

4. To study the effect of long-term use of dextranase on gingival status.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Doran D. Zinner	281-14-0041	2
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Melquiades Gavillan	581-68-6179	36
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Howard University School of Dentistry
Washington, D. C. 20005

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH 71-2041	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
July, 1970	[X] AD HOC COMMITTEE [ ] STANDING COMMITTEE	Dr. Horace M. Stiles

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

1. The Contractor will supply all necessary personnel and facilities and exert his best efforts to conduct a field trial study of a dental sealant material designed to reduce pit and fissure caries. The field trial will involve a study population of approximately 1000 children, to be located and selected by the Contractor in Washington, D. C., and shall be conducted in accordance with the NIDR Standard Protocol for Adhesive Sealant Study, dated October 6, 1970.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Virgil E. Whitehurst, B.S.,M.S.,Ph.D.		8
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Clarence Chapman, D.D.S.		20
	2. Aly E. Bastawi, B.D.S.,M.S.D.		12
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
University of Puerto Rico
Virgin Islands

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2062 S.A. #3	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
10/14/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Ralph A. Frew

SECTION II – FOR NEW, RENEWAL, CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

1. To further investigate the anticaries effect of an adhesive sealant material.

2. To determine the durability of the adhesive sealant material.

3. To gain information on the time required and the difficulty involved in the application of the material under typical field conditions.

4. To evaluate the caries retarding effect of the material when utilized as a sealant for incipient carious lesions occurring in pit and fissure sites.

5. To study the subsequent rate, with respect to caries incidence, of tooth surface sites from which the sealant material is lost.

6. To assess the feasibility of application of the sealant by minimally-trained non-professional, personnel.

Proposed course is completion of the sealant applications during this and the next fiscal; follow-up examinations at 6 mos. intervals for each subject, for the balance of the four-year project period.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (*Last, first, initial*)	SOCIAL SECURITY NUMBER	TIME (*Hrs. per week-in whole hrs.*)
PROJECT DIRECTOR *(Limit to 1)*	Norman O. Harris	not available	4
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Robert Silverman	202-26-7803	40
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
Health Research, Inc.
Albany, New York

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH-NIDR-71-2093	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
9/4/70	[ ] AD HOC COMMITTEE [x] STANDING COMMITTEE	Dr. Ralph A. Frew

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 2,870

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

To test the ability of the adhesive sealant to prevent new carious lesions from forming in pits and fissures of selected caries-free teeth in a large-scale clinical trial over a four-year period on approximately 3,000 first grade children. The durability of the sealant will also be measured. In addition, the time required to place the sealant on the teeth will be recorded.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. Naham C. Cons, Director, Bureau of Dental Health		
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. Sydney T. Pollard, Assoc. Proj. Dir.		
	2. Dr. Gary S. Leske, Field Director		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

Howard University

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**		INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2108		DE-2-01
DATE OF PRIMARY REVIEW	CHECK ONE: [X] AD HOC COMMITTEE [ ] STANDING COMMITTEE	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
Jan. 18, 1971		Baer, Paul N.

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The objective of the contract is to study the causative factors of periodontal disease in adolescents by (1) determining whether patients between ages 11-23 can be separated into several groups - those who are very resistant to the disease, those who are moderately resistant, and those who are highly susceptible, (2) comparing the incidence and severity of periodontal disease in families of patients with periodontosis with those classified as being within normal limits, and (3) determining whether the pre-eruption oral mileu of the area of the primary 2nd premolar exerts demonstrable influence on the periodontal condition of the permanent 1st molar.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Henry, Joseph L.	Unknown	As required
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR Beckman Instruments, Inc.
2500 Harbor Boulevard
Fullerton, California 92634

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2329 6/30/71-6/29/72	DE 1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Earl W. Gardner

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 8,825

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert best efforts to produce enzymes, with specific ability to degrade the branched polysaccharide dextrans present in human plaque.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Don L. Isenberg	456-48-6855	8
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Randall S. Davis	268-40-1782	24
	2. Dr. Edward H. C. Sie	405--36-3445	4
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☒ New ☐ Terminal
☐ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Southern Illinois University
School of Dental Medicine
Edwardsville, Illinois 62025

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2330 6/30/71-6/29/72	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Earl W. Gardner

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert best efforts to isolate and purify dextransucrases, levansucrases, and glycosidic hydrolases, from cariogenic streptococci, which will be investigated for their effectiveness as immunizing agents to reduce experimental dental caries.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Arthur N. Bahn	013-20-4265	20
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. James A. Hayashi	333-22-6648	5
	2. Dr. Barney Kadis	505-24-4136	5
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
☒ New ☐ Terminal
☐ Renewal ☐ Change

SECTION I FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: University of Minnesota (Regents of the)
School of Dentistry
Hennepin County, Minneapolis, Minnesota 55455

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2331 6/29/71 - 6/28/72	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Earl W. Gardner

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert best efforts to investigate unique features of the membrane-associated phosphotransferase sugar uptake system of oral cariogenic bacterial and to analyze for antimicrobials which could inhibit this system.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Charles F. Schachtele	474-46-5754	12
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. John A. Mayo	474-46-7000	20
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Medical College of Georgia, School of Dentistry
Department of Oral Biology
August, Richmond County, Georgia 30902

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2332	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	[ ] AD HOC COMMITTEE [x] STANDING COMMITTEE	Dr. Earl W. Gardner

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert its best efforts to search for and obtain potential anticaries agents from pharmaceutical companies and conduct in vitro and in vivo tests of the anticaries efficacy of these agents.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. George W. Burnett		16
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Louis P. Gangarosa		8
	2. Dr. George S. Schuster		4
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminol
[ ] Renewol [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Forsyth Dental Center
140 Fenway
Boston, Massachusetts 02115

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2333 6/28/71-6/27/72	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Earl W. Gardner

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert best efforts to investigate the effects of specifically induced salivary antibody to Streptococcus mutans upon plaque bacteria and dental caries in gnotobiotic rats and conventional hamsters.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Martin A. Taubman	102-32-1548	4
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Forsyth Dental Center
104 The Fenway
Boston, Massachusetts 02115

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2375	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/31/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. James P. Carlos

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The Contractor will:

1. The relative effectiveness of semi annual 3-minute topical application of (1) 0.06M NH_4F. pH4.4 preceeded by .05M H_3PO_4 (1-minute) and (2) NaF, 1.2% in 0.1M H_3PO_4, pH 3.2, in the control of human dental caries.

2. Fluoride uptake in teeth of subjects receiving the foregoing treatments and to relate fluoride uptake to caries experience on a group basis.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Paul F. DePaola		as necessary
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Emil Klinkenberg (Examiner)		4
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR University of Minnesota
2610 University Avenue
St. Paul, Minnesota 55114

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2376 6/30/71-6/29/72	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/29/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. William R. Sanslone

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The scope and nature of this clinical research study is directed toward achieving the following objectives:

1. The development of a precise clinical method or procedure for evaluating the effects of diet variations upon microbial and biochemical composition of human plaque.

2. The estimation of the relative effects of sucrose upon plaque formation in human subjects.

3. The measurement of effects of sodium trimetaphosphate upon plaque formation in the presence as well as the absence of sucrose.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Lars E. A. Folke	110-38-7493	12
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Robert S. Harris	013-26-0659	20
	2. Dr. William F. Liljemark	476-46-6230	20
	3. Dr. Charles F. Schactele	474-46-5754	4

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: University of Texas, Dental Branch
6516 John Freeman Avenue, Texas Medical Center
P. O. Box 20068, Houston, Texas 77025

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2377	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/30/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Horace M. Stiles

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Prime objectives are:

1. Clarify the saliva-microbial-dental caries relationship by:

   a. Delineating the general characteristics of the oral microbial population changes in patients with radiation induced xerostomia.

   b. Identifying the specific changes in the occurence and numbers of those microorganisms which have been implicated in the caries process.

   c. Elucidating the effect of caries preventive agents and procedures on the oral microflora in patients with radiation induced xerostomia.

2. Establish a human model system for the rapid screening of anticaries agents in the presence of an unusally potent and ever present caries challenge.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Samuel Dreizen		4
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Lee R. Brown, Jr.		14
	2. Dr. Joe B. Drane		As needed
	3. Dr. Richard E. Jesse		As needed

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Forsyth Dental Center
140 The Fenway
Boston, Massachusetts 02115

CONTRACT NUMBER *Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2379	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/31/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. James P. Carlos

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The Contractor will:

1. Compare the relative caries inhibitory effect of supervised, daily, one-minute mouth rinses in school with (a) 5 ml of NH_4F, pH4.4. containing 5 mg of F ion, and (b) 5 ml of neutral NaF containing 5 mg of F ion.

2. Determine fluoride uptake in subjects receiving the foregoing treatments and to relate fluoride uptake to caries experience on a group basis.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Paul F. DePaola		as necessary
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dental Examiner to be Named		4
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Bronch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
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☐ Renewal ☒ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
University of Alabama
Birmingham, Alabama 34322

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-71-2380	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/29/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Ralph Frew

SECTION II – FOR NEW, RENEWAL, CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Objective of study is to establish and measure the antimicrobial and anticaries activity of Sodium Trimetaphosphate (STMP) when topically applied to the dentition of children in a chewing gum vehicle. The gum will be distributed to approximately 600 children participants on a systematic basis with oral examinations to be conducted prior to the study and at 6 month intervals thereafter. Both clinical and radiographic results will be observed and recorded by the Contractor, and transmitted to NIDR for processing and anlysis of the data in-house. All children will receive a dental prophylaxis prior to each examination.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Finn, Sidney B.	521-48-4861	10
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Keele, B.B.	522-52-7064	12
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Bronch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminol
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SECTION I FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Eastman Dental Center
800 East Main Street
Rochester (Monroe County), New York 14603

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**: NIH-NIDR 71-2381

INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*: DE-1-01

DATE OF PRIMARY REVIEW: 3/29/71

CHECK ONE:
[ ] AD HOC COMMITTEE
[X] STANDING COMMITTEE

NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE: Dr. William R. Sanslone

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will attempt to relate trace elements of teeth to their caries susceptibility by:

1. Selecting human teeth from geographic areas of high and low caries prevalence to determine the approximate concentrations in enamel and dentin of the major trace elements, together with calcium and phosphorus.

2. Analyses from residents of Colorado, Texas, New York, Ohio, Maine, and California will be reported.

3. Sufficient samples will be analyzed to provide information on intra-tissue distribution of elements so that a relationship can be extablished between trace element composition and resistance to caries.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Fred L. Losee		20
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Marguerite F. Little		10
	2. Marjorie Grant Whiting		20
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
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SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Harvard School of Dental Medicine
188 Longwood Avenue
Boston, Massachusetts 02115

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2382	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/29/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. William Sanslone

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will exert best efforts to estimate caries-producing potentials of human foods and their potential role as caries of possible caries-inhibiting agents by assays with experimental rodents.

Contractor will:

Develop in rodents as assay which will utilize programmed feeder technique to measure caries-producing potential of human foods.

Utilize assay to estimate caries-producing potentials of commonly used human foodstuffs.

Evaluate efficacy of adding foodstuffs with high caries potential, agents believed to be caries inhibitors, such as sodium trimetaphosphate, calcium sucrose phosphate, & any others which may eventually be utilized in human diets.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. James H. Shaw, Ph.D.		8
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RESEARCH CONTRACTS
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SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Midwest Research Institute
425 Volker Boulevard
Kansas City, Missouri 64110

CONTRACT NUMBER *Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2383	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/29/71	[ ] AD HOC COMMITTEE [x] STANDING COMMITTEE	Dr. Robert J. McCune

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE*	$ 4,527

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Various experimental polymers shall be prepared and screened as dental restorative materials potentially useful as elastomeric liners or composite filling base and shall also perform as an adhesive.

The contractor shall select a series of monomers for exploratory copolymerization with the higher alkyl acrylates. The copolymers shall be characterized and screened for their elasticity or toughness, stability in aqueous media, and their adhesion to tooth structure. As the work progresses, suitable modifications shall be made in the monomer composition or selection of monomers to bring about improvement in the properties on the basis of correlations that can be established. When the best polymer system with respect to these requirements has been found, polymerization variables shall be optimized to further improve polymer properties such as tensile strength, elongation and hardness.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Mr. L. W. Breed		12
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Mr. Howard Christie		6
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Forsyth Dental Center
140 Fenway
Boston, Massachusetts 02115

CONTRACT NUMBER *(Include Supplemental Agreement No., if any.)*: NIH-NIDR-71-2384

INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*: DE-1-01

DATE OF PRIMARY REVIEW: 3/29/71

CHECK ONE:
[ ] AD HOC COMMITTEE
[X] STANDING COMMITTEE

NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE: Dr. William Sanslone

SECTION II – FOR NEW, RENE CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will analyze for presence of various trace elements samples obtained from two groups of people having marked differences in caries prevalence not due to fluoride. He will attempt to associate presence of these elements with resistance to caries to determine if certain trace elements in diet may potentiate anti-cariogenic effect of fluoride.

Select for analysis samples of water, soil, food, saliva, and teeth which have been obtained from Colombia, S.A. Analyze these samples for presence of as many of the major trace elements as possible. Relate these elements to caries prevalence in these two communities.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Robert Loring Glass		4
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
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[x] New [ ] Terminol
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SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR Associated Biomedic Systems, Inc.
872 Main Street
Buffalo, New York 14202

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2385	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
11/11/70	[ ] AD HOC COMMITTEE [x] STANOING COMMITTEE	Dr. Jack H. Pincus

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE*	$4,692

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

This contract effort will provide for the production and origination of cell lines and the isolation of histocompatibility antigens from lymphoid cell lines. It will include furnishing cell lines derived from human and mouse cells, certification as to percent viability, establishment of new cell lines, preparation and supplying of hist-compatibility antigens including purity certifications, and providing mouse lymphocytes and tumor cells as requested by the Government Project Officer.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Benjamin W. Papermaster		6
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Bruce Maurer		7
	2.		
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

Battelle Memorial Institute, P. O. Box 999, Richland, Washington 99352

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2386 6/30/71-6/29/71	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
11/11/70	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Robert J. McCune

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 6,000

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The contractor will study at least four materials as dental implants. These will include Titanium, void metal composite; Titanium, powder metallurgy product; Alumina porcelain; and Magnesium aluminate spinel. These materials will be characterized by physical tests and implants designed to optimize desirable characteristics will be implanted in swine jaws and subjected to clinical and microscopic examinations to determine their clinical efficacy. A special scanning electron microscope examination of frozen-fractured specimens of the bone material interface will be performed. An important goal will be optimization of root material porosity to allow inward tissue growth and the achievement of implant stability.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Mr. Robert P. Marshall		20 hours for entire year
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. R. E. Westerman		34 hrs. week
	2. Dr. J. J. Rasmussen		24 hrs. week
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: Columbia University
600 West 168th Street
New York, New York 10032

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH-NIDR-71-2387	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
1/27/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Mr. Rickley S. Sennig

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor shall exert best efforts in studying analytic procedures for data of the type collected by NIDR during dental caries clinical trials and in reporting the results of these studies. This will include the testing of existing data for degree of adherence to any model assumptions, and identification of the most appropriate analytic method under several variations in experimental design. The ultimate result will be the development of a document encompassing the exposition of validated methodologies as well as standardized methods of data presentation including any appropriate charts and tables.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. John W. Fertig		4
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. Neal W. Chilton		4
	2. Dr. Andre O. Varma		8
	3.		

NIH-1688-1
Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
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RESEARCH CONTRACTS
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☐ Renewal ☐ Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
University of Utah
Salt Lake City, Utah 84112

"Environmental Stress on Teeth"

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-71-2388 6/16/71-6/15/72	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	Dr. Robert J. McCune

SECTION II – FOR NEW, RENEWAL, CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor will perform temperature cycling tests on teeth filled with specifically shaped fillings designed to stimulate commonly used filling configurations. Teeth will be inspected for cracks by several methods with the fluorescent dye technique. Calculations of time-dependent temperature and stress distribution will be related using the appropriate computer systems. The results of both the experimental and analytical programs will be analyzed to determine if improvement can be made in cavity preparation and choice of material with emphasis on thermal considerations.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. W. S. Brown		8
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. H. R. Jacobs		4
	2. R. F. Boehm		4
	3. Dr. John Chun		4

NIH-1688-1
Rev. 11-70

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RESEARCH CONTRACTS
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[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR Research Triangle Institute
P. O. Box 12194
Research Triangle Park, North Carolina 27709

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH-NIDR-71-2389 6/29/71-6/28/72	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
1/27/71	[ ] AD HOC COMMITTEE [x] STANDING COMMITTEE	Mr. Rickley S. Senning

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $ 2,790

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

This project has three prime objectives which are to:

1. study alternative approaches to the analysis of the data on dental caries of the type collected by NIDR under several variations in experimental designs which include simple and stratified random sampling in the selection of control and treatment groups.

2. Identify and provide detailed expositions of the most appropriate analytic methods.

3. To consider new methods for the analysis of caries data so that the selective effect of treatment by surface type may be investigated and the possibility of recording data from selected surfaces and/or teeth may be explored.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. Babubhai V. Shah		TOTAL ANNUAL TIME: 3 weeks
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. W. K. Poole		8 weeks
	2. Dr. A. V. Rao		8 weeks
	3. Mr. T. D. Hartwell		8 weeks

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Rev. 11-70

* Research Contracts Branch will complete this item if it is unknown to the Project Director

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RESEARCH CONTRACTS
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CHECK ONE
[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: World Health Organization
Geneva, Switzerland

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-72-2003	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
	[ ] AD HOC COMMITTEE [ ] STANDING COMMITTEE	Dr. Charles J. Donnelly

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

1. To test hypothesis formulated on the basis of associations with dental caries prevalence defined for primitive village populations in the territory of Papua and New Guinea.

2. To confirm, expand, or reject certain associations suggested or suspected from previous studies in that territory.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. David E. Barmes		
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
	3.		

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Rev. 11-70

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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[x] New [ ] Terminol
[ ] Renewol [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: THE ROYAL DENTAL COLLEGE
Department of Periodontology
Aarhus, Denmark

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH-NIDR-72-2005	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
11/11/70	[ ] AD HOC COMMITTEE [x] STANDING COMMITTEE	Dr. James P. Carlos

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The Contractor shall conduct a controlled clinical study to (1) test the long term effect of chlorhexidine on the development of dental plaque, caries and periodontal changes, (2) examine the microflora of the saliva, gingiva and tooth surfaces during such treatment, and (3) assess possible systemic and local side effects of long term use of chlorhexidine.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. Harald Loe	(foreign) N.A.	as required
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. C. Rindom Schiott	" N.A.	as required
	2. Dr. Leif Glavand	" N.A.	as required
	3. Dr. S. Borglun Jenson	" N.A.	as required

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Rev. 11-70

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

UNIVERSITY OF ALABAMA

CONTRACT NUMBER *(Include Supplemental Agreement No., any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-72-2030	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
7/27/71	☐ AD HOC COMMITTEE ☒ STANDING COMMITTEE	DR. EARL GARDNER

SECTION II – FOR NEW, RENE CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

1. The Contractor will perform:

   a. A thorough and complete comparative evaluation, in young human subjects, of the test slab lesions as contrasted to natural lesions, utilizing all available procedures for measurement.

   b. A thorough and complete comparative evaluation, in young human subjects, of the microbial and biochemical compositions of test slab versus natural plaque.

   c. After the intraoral cariogenicity system has been sufficiently validated, in the opinion of the Project Officer, a series of test variables may be imposed upon the model system to determine their relation to the promotion or inhibition of caries development.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Koulourides, Theodore	419-56-6331	13 hours
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Sandham, H. James	420-74-5758	13 hours
	2. Keller, Stanley E.	020-14-8781	4 hours
	3. Bodden, Rupert	722-05-0493	4 hours

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Rev. 11-70

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RESEARCH CONTRACTS
SUPPLEMENTAL INFORMATION RECORD

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
Eastman Dental Center

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-72-2039	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/29/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. William R. Sanslone

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The contractor proposes to:

1. To define which foodstuffs are more harmful or less harmful to the teeth in regard to caries and will test the effect of using the less harmful ones.

2. To provide snack materials to replace those of high cariogenicity.

3. To evaluate the acceptability of these snack materials on school children.

4. To initiate a study of these snack materials on school children designed to determine their effect on dental caries.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. Basil G. Bibby		32
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Sheila Mundortf		40
	2.		
	3.		

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* Research Contracts Branch will complete this item if it is unknown to the Project Director

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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[x] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I - FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR
American Dental Association, 211 East Chicago Avenue, Chicago, Illinois 60611

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR 72-2045	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
3/31/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Samuel Kakehashi

SECTION II - FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The Contractor proposes to:

a. Clinically test the validity and reproducibility of utilizing an ultraviolet fluorescent technique for the early detection of carious lesions.

b. Establish baseline information as to the level of normal fluorescence of the dentition.

c. Localize these areas and measure the rate of demineralization or alterations of tooth surfaces with the aid of fluorescence.

d. Test the applicability of the fluorescent technique in detecting carious alterations on all surfaces of the clinical crown.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	Dr. John J. Hefferren		10
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1. Dr. Harvey W. Lyon		6
	2. Dr. Robert O. Cooley, Clinician		8
	3.		

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[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR: University of Miami
Coral Cables, Florida 33124

CONTRACT NUMBER (Include Supplemental Agreement No., if any)*	INSTITUTE PROGRAM I.D. CODE (See NIH Manual 2850-1)
NIH-NIDR-72-2400	DE-1-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER (Last, First, M.I.) LIST ONE
6/15/71	[ ] AD HOC COMMITTEE [X] STANDING COMMITTEE	Dr. Roald J. Shern

SECTION II – FOR NEW, RENEWAL CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: (100 words or less)
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

Contractor shall provide all necessary staff, facilities and populations to carry on a field trial of a topical fluoride study to:

1. assess the level of enamel fluoride attained after a series of treatments of topical gel to teeth of children consuming fluoride deficient water,

2. to assess the rate of loss of fluoride from enamel after treatments have been completed, and

3. to assess the residual anti-caries effect of 3 short treatment regimens.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME (Last, first, initial)	SOCIAL SECURITY NUMBER	TIME (Hrs. per week-in whole hrs.)
PROJECT DIRECTOR (Limit to 1)	Dr. Doran D. Zinner	281-14-0041	2
OTHER SENIOR SCIENTISTS (Limit to 3)	1. Dr. Luis F. Duany	261-72-6992	4
	2. Dr. Julia C. Mena	263-70-1896	8
	3. Dr. Melquiades Gavillan	581-68-6179	4

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[X] New [ ] Terminal
[ ] Renewal [ ] Change

SECTION I – FILL IN THIS INFORMATION WITH EVERY SUBMITTAL

NAME OF CONTRACTOR

Pennsylvania State University

CONTRACT NUMBER *(Include Supplemental Agreement No., if any)**	INSTITUTE PROGRAM I.D. CODE *(See NIH Manual 2850-1)*
NIH-NIDR-72-2401 2/27/72-2/26/73	DE-2-01

DATE OF PRIMARY REVIEW	CHECK ONE:	NAME OF NIH PROJECT OFFICER *(Last, First, M.I.)* LIST ONE
7/71	[X] AD HOC COMMITTEE [ ] STANDING COMMITTEE	Dr. James F. Bosma

SECTION II – FOR NEW, RENEW CONTRACT, OR CHANGE

CONTRACT FIXED FEE, IF COST PLUS FIXED FEE* ..... $

SUMMARY OF CONTRACT OBJECTIVES AND WORK SCOPE: *(100 words or less)*
FOR NEW CONTRACTS: A Xerox copy of the work scope defined within the contract is permissible; if 100 words or less.
FOR RENEWAL CONTRACTS OR CHANGES: Complete only if changed from prior contract period.

The contractor with his laboratory staff and appropriate associates from other Departments of his University will select and breed monkeys, obtain fetuses at selected gestational ages by caesarian section, evaluate the stage of their development by appropriate qualitative and quantitative criteria, and obtain oral tissues at standard sites.

Will prepare sample tissues for microscopic and ultramicroscopic study, employing methods standard in that laboratory.

Will study and describe the histological progressions of development, as evidenced in the specimens prepared in this project.

INVESTIGATOR INFORMATION (Complete for new contracts or for subsequent changes - otherwise leave blank):

	NAME *(Last, first, initial)*	SOCIAL SECURITY NUMBER	TIME *(Hrs. per week-in whole hrs.)*
PROJECT DIRECTOR *(Limit to 1)*	B. L. Munger		4 hrs.
OTHER SENIOR SCIENTISTS *(Limit to 3)*	1.		
	2.		
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* Research Contracts Branch will complete this item if it is unknown to the Project Director