Annual
Report

National Institute of Neurological and Communicative Disorders and Stroke

Annual Report

Fiscal Year 1982

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

ANNUAL REPORT

October 1, 1981 through September 30, 1982

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents*

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*A detailed Table of Contents for each program area will be found immediately following the TAB indicator.

Alphabetical Listing of NINCDS Principal Investigators

Alphabetical Listing of NINCDS Principal Investigators - (Cont'd)

INTRAMURAL RESEARCH PROJECTS
Numerical Inventory

NEW INITIATIVES FOR FY 1982

TAB 1 -- OFFICE OF THE DIRECTOR -- OD/NINCDS (INCLUDES: OD, EEO, OSHR & OPA)

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Office of the Director, NINCDS

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report of the Acting Director
of the
National Institute of Neurological and
Communicative Disorders and Stroke
October 1, 1981 through September 30, 1982

Fiscal Year 1982 has been characterized by (1) a continuation of the search for an Institute Director with a resulting delay in several areas of overall planning and program consideration, (2) more than usual difficulty in the recruitment of key scientific staff in the intramural program and (3) critical changes in the philosophy of extramural research funding because of the most severe competition for available funds in the history of the Institute.

With the retirement of the Institute Director as of February 1, 1981, an Acting Director and Acting Deputy Director have borne the responsibility for Institute leadership. This has included presentation of the Institute's budget to the Congress on each of 2 years and the preparation of the Institute's budget request to the Department for a 3rd year. Major changes in Institute organization and in the recruitment of the management team were again postponed; however, with the approval of the Director, National Institutes of Health (NIH), selected critical changes were initiated. These included: the recruitment of a Chief of the Office of Planning and Analysis (OPA), (formerly the Office of Program Planning and Evaluation); discontinuation of the pilot program to develop and implement a new all Institute program information system (PINS) and designation of the former extramural program information system as the overall Institute unit; a Scientific Program Advisory Committee (SPAC) as the scientific advisory panel for extramural research planning; forwarding a request to the Department for reorganization of the Extramural Neurological Disorders Program into two Programs (the Convulsive, Developmental, and Neuromuscular Disorders Program, CDNDP, and the Demyelinating, Atrophic, and Dementing Disorders Program, DADDP); the appointment of a Director, CDNDP, and an Acting Director, DADDP; completion of a scientific merit and policy review of the Institute's Guam research program; completion of a scientifc merit and policy review of the Institute's neural prosthesis program; completion of a scientific merit and policy review of the Institute's anti-convulsant drug development program; and completion of a scientific merit and policy review of the Institute's Venezuelan Lake Maracaibo Huntington's Disease research endeavor. In compliance with an order from the Secretary, search procedures have been initiated for an NINCDS Associate Director for Neurological Disorders and for an NINCDS Associate Director for Communicative Disorders.

The Institute's intramural research program continues to be characterized by a continuing high level of research productivity in some areas and an acceptable but necessary reconsideration of research organization and operation in other areas. The recently developed neurosurgical research program is now well established and functioning well. After an extended search, a Chief of the Laboratory of Neurophysiology has been appointed and is doing well in focusing his laboratory's research activities at high levels of scientific priority. However, recruitment for other key scientific leadership positions have been unsuccessful; these include leaders of the Institute's intramural endeavors for epilepsy, for clinical communicative disorders,

and for positron emission tomography. The non-competitive federal salary and the inability to offer recruitment possibilities (additional slots) are the major reasons given by candidates for declining appointment to these positions.

The Institute is beginning to occupy the new space assigned to it in the NIH Ambulatory Care Research Facility. The lengthy delay for availability of the space, and the not unexpected continuing frustrations in completing the necessary physical moves have made the occupancy a difficult experience. Because of several years of limitation of intramural resources (slots, other object funds, station support contract funds), Fiscal Year 1983 will be characterized by additional steps to decrease resources to laboratories not of the highest productivity. A plan has been developed by the Institute's Intramural Director and will be implemented by him. Several research prizes of national and international renown have been won by NINCDS intramural scientists including the Pisano Award and the Lasker Award.

Despite modest increases in the availability of research grant funds, the NINCDS research grant program has had its most difficult year in Institute history. The competitive funding rate has fallen to one of its lowest funding levels; "commitments" have been reduced by formula cuts; and competing grants have been awarded at marked reductions from levels recommended. These administrative steps have had a serious impact on the recruitment of new scientists to areas of Institute responsibility and on the morale of the present cadre of skilled scientists. The Institute staff is working closely with the NINCDS National Advisory Council to identify and explore philosophical and administrative alternatives to stabilize the research grant program for the next decade. Unfortunately, one product of the difficult extramural funding issues is a divisiveness developing between extramural grantees and intramural scientists who each believe the other is receiving favored treatments; steps are being taken to inform all parties of the total status and to encourage closer interactions and cooperation.

In conclusion, it has been a privilege to serve the Institute as Acting Director for Fiscal Year 1982. All Officers of the Institute and members of the staff have my gratitude for their assistance and cooperation.

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Equal Employment Opportunity Office
Office of the Director
National Institute of Neurological and
Communicative Disorders and Stroke

INTRODUCTION

The National Institute of Neurological and Communicative Disorders and Stroke's (NINCDS) equal opportunity, affirmative action and civil rights activities are centered in the Equal Employment Opportunity Office. This Office serves as principal advisory to the Director of the Institute and managers at all levels concerning positive application and enforcement of Affirmative Action and Civil Rights policies of the Federal government. It is responsible for coordinating, evaluating and monitoring the enforcement of the 1964 Civil Rights Act and Executive Order 11246 in matters concerning the Institute's contracts and grants, coordinating the implementation of the Black College Initiatives (Executive Order 12320), and developing and implementing programs supportive of the Minority Biomedical Research Support (MBRS) and Minority Access to Research Careers (MARC) Programs. The Office also manages the NINCDS Community Outreach Programs to increase the representation of minorities and women in biomedical research, particularly the neurosciences. The Institute has an EEO Advisory Committee that provides advice to the Director, NINCDS, on all matters relating to Equal Employment Opportunity, and an EEO Counselor that counsels employees and applicants who believe they have been discriminated against, and representatives to the NIH Federal Women's Program and the Handicapped Employees Advisory Committee.

The Institute continues to implement a viable affirmative action program to increase the representation of minorities and women in its work force. The Multi-Year Affirmative Action Plan will include specific actions and strategies that will facilitate the recruitment and placement of minorities in the Medical Staff Fellowship Program, Research Staff Fellowship Program, biological and physical sciences and top management positions. The Plan will also include mechanisms to increase NINCDS' support to Historically Black Colleges and Universities.

SIGNIFICANT NINCDS AFFIRMATIVE ACTION ACCOMPLISHMENTS AND INITIATIVES IN FY'82

Promotions

In FY'82, fifty-six employees were awarded promotions in the Institute. Eleven (or 23%) were minorities and thirty-six (or 64%) were non-minority females. Twenty employees received promotions at grade levels GS-9 and above, five were minorities and twelve were females.

Honors and Awards

Forty-two employees received recognition under the Federal Incentive Awards Program in FY'82. Approximately six (or 14%) were minorities and twenty-nine (or 69%) were non-minority females.

MINORITY BIOMEDICAL RESEARCH SUPPORT (MBRS) AND MINORITY ACCESS TO RESERCH CAREERS (MARC) PROGRAMS

In order to increase the number of minorities undertaking research in the neurosciences, the NINCDS within the past few years established cooperative agreements to support components of the Minority Biomedical Research Support (MBRS) and Minority Access to Research Careers (MARC) Programs that relate to the overall NINCDS mission.

The funds NINCDS awards through MBRS and MARC Programs strengthen the neuroscience research capabilities of minority institutions of higher education. This support also helps to develop minority neuroscientists, and enables the NINCDS to identify and support meritorious projects that have been proposed by minority investigators.

In FY'82, the NINCDS awarded $150,000 to support MBRS grants at the following schools: South Carolina State College, University of New Mexico, Howard University and City College of New York.

Under the NIH Summer Program, the Institute selected eight students (4 MBRS students and 4 MARC Honors students) for positions in the Institute's research laboratories.

NIH SUMMER RESEARCH FELLOWSHIP PROGRAM

In FY'82, NIH initiated the Summer Research Fellowship Program, a biomedical research training program available to medical and dental students. Eleven medical students from various medical schools throughout the country were selected for training positions in the NINCDS Intramural Research Program. Six (or 55%) were minority medical students and three (or 27%) were non-minority female medical students. To correct the underrepresentation of minorities and women in the Medical Staff Fellowship Program, aggressive recruitment and placement of minorities and women in this program will continue to be an affirmative action goal of the NINCDS.

SUPPORT TO HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Executive Order 12320, dated September 15, 1981, directs each Federal agency to increase the participation of Historically Black Colleges and Universities in Federally sponsored programs. Initiatives implemented in FY'82 in NINCDS were:

A. Ten students from seven Historically Black Colleges were selected for summer positions in the Institute.

B. Two Minority Biomedical Research Support grants and two research grants were awarded to Historically Black Colleges.

C. Institute staff members conducted seminars concerning NINCDS programs and activities at Delaware State College, Dover, Delaware; Langston University, Langston, Oklahoma; and Howard University School of Medicine, Washington, D. C.

D. Four medical students from Howard University School of Medicine were selected for reserch training positions under the NIH Summer Research Fellowship Program.

E. As part of the Summer Externship Program for medical students at Provident Hospital in Baltimore, Maryland, eight students from Meharry Medical College and Morehouse College of Medicine were selected for clinical research training positions in the Institute.

COMMUNITY OUTREACH ACTIVITIES

Staff members from the Institute participated in the following workshops and symposiums to promote the participation of minorities in the neurosciences:

A. The Minority Biomedical Research Support Symposium;

B. The Student National Medical Association Conference;

C. The National Medical Association Scientific Meeting; and

D. Graduate and Professional Opportunities Career Day Program at the University of Minnesota, including a meeting with Black and Hispanic medical and dental students.

NEW INITIATIVES

The Institute in FY'82 implemented the following two initiatives to increase the representation of minorities in the neurosciences:

A. In an effort to increase participation of minority students in the neurosciences, the NINCDS has awarded a three-year grant to the Society for Neuroscience for the establishment of a program that will provide funds for minority students and scientists to attend annual meetings of the Society.

B. In order to increase the participation of Hispanics in the Summer Program and other reserch training programs in the NINCDS, the Institute's EEO Officer and Personnel Officer conducted a series of seminars at: (a) University of New Mexico; (b) California State University; (c) East Los Angeles College; and (d) University of California, San Diego. Meetings were held at each school with MBRS and MARC students to provide information and discussions concerning career and training opportunities in biomedical research at the NIH.

Three Hispanic students from the University of New Mexico and a MARC Honors student from California State University were appointed to summer positions in the Institute's research laboratories. One student from the University of California, San Diego accepted a position with the National Heart, Lung and Blood Institute.

NIH EEO PROGRAM

Assisting in the development and implementation of NIH Affirmative Action and Civil Rights Programs continues to be an important function of the Institute's EEO Office. In FY'82, the Office participated in the following functions at the NIH level:

A. Mr. Levon O. Parker, the Institute's EEO Officer, was selected to chair the NIH Committee on Black College Initiatives. The Committee was formed as part of the NIH Civil Rights Plan to define and implement the NIH role in the implementation of Executive Order 12320 concerning Historically Black Colleges and Universities.

B. In conjunction with three other Institutes, conducted a seminar and laboratory tour for students in the United Negro College Fund Premedical Summer Institute; science students from Morgan State University; participants in the North Carolina Health Manpower Development Program; and the Prehealth Careers Program at Benedict College, South Carolina.

C. The EEO Officer participated in the development of mechanisms to monitor job selection at the NIH.

D. The Office and other staff members of the Institute participated in the first NIH Affirmative Action Recruitment Conference. The objectives of the conference were: (1) to provide a forum in which NIH program officials could meet with representatives from selected institutions with significant minority and female enrollments; (2) to familiarize the academic community with the staffing needs of the NIH, especially in the scientific areas, with particular emphasis on those occupational categories in which minorities and women are underrepresented; and (3) to develop a network of resources in the academic community that will identify potential applicants for positions at the NIH.

EEO ADIVSORY COMMITTEE

The Institute's EEO Advisory Committee played an important role in the development and implementation of NINCDS' EEO/Affirmative Action Programs in FY'82. Some activities of the Committee this past year were:

A. In conjunction with the EEO Office and the Personnel Office, the Committee initiated a new information sheet entitled "EEO/Personnel News Briefs." This newsletter is an effort to keep employees abreast of current developments in EEO and Personnel.

B. Sponsored meetings in two program areas to give employees an opportunity to discuss concerns and issues with top management.

C. Organized the Annual NINCDS All Employees' Meeting.

ANNUAL REPORT
October 1, 1981 through September 30, 1982

Office of Scientific and Health Reports
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

Within the National Institute of Neurological and Communicative Disorders and Stroke, dissemination of research information to the public is chiefly the responsibility of the Office of Scientific and Health Reports (OSHR). This Office advises the Director and the executive staff on ways to effectively report results of research conducted and supported by the Institute. Reporting tasks range from simply mailing a pamphlet in response to an inquiry to writing and coordinating technical state-of-the art reports.

The OSHR consists of two main sections, Public Inquiries and Scientific Publications, and a media liaison effort carried out by the Office deputy chief.

OSHR staffing remained stable for most of this fiscal year, with the Public Inquiries Section benefiting from its strongest staffing in years. Two summer interns with previous experience in science writing also helped give the office stronger capabilities than had been available in previous summers.

The only major staff change occurred in the Scientific Publications Section, where Robert Hinkel, who had been with the OSHR for 17 years in a 27-year career at NIH, retired at the end of June. Mr. Hinkel had been chief of the Scientific Publications Section since 1971. His departure left the Section with only one full-time writer/editor in an office that had had 3 the previous year. The impact of this severe staff shortage was mitigated somewhat when a well-trained science writer was hired as a summer intern for the Section, and by the continuing moratorium on Department of Health and Human Services publications. In August, however, permission was obtained to proceed with 3 new Hope Through Research pamphlets that were part of the FY82 publications plan. The Acting Director, NINCDS, agreed that OSHR should bring the Scientific Publications Section back to full staff, and the office began taking the steps necessary to achieve this objective.

The DHHS-wide moratorium, in effect since May 1981, seriously disrupted progress in revising outdated NINCDS publications, including the Hope Through Research series of information pamphlets for the public. Work was allowed to continue on five previously approved pamphlets that originally had target publication dates in FY81 but that had fallen behind schedule. All five were published in FY82. However, it became increasingly difficult to manage the Section effectively, since there was no assurance that planned projects would be approved by DHHS. As a result, all FY82 projects are being moved to the FY83 publications schedule. In effect, then, the OSHR has "lost" one publishing year. If the recent permissions can be seen as a return to allowing the Institute to publish in the public interest, then it may be possible to pick up the interrupted schedule and maintain good productivity for the next three years or so until all outdated material has been revised.

Public Inquiries Section

The Public Inquiries Section responds to written and telephone inquiries concerning some 600 neurological, communicative, and sensory disorders as well as to questions about Institute programs and policies. Many of the inquiries involve complex subject matter, requiring coordination with intramural scientists and grantees to ensure that replies are as responsive as possible. Inquiries concerning policies and programs sometimes must be coordinated with Institute officials and the NIH and DHHS Secretariat.

During FY82, patients with disorders of the nervous system, and their families and friends, were by far the largest requesters of information. They asked primarily about effective treatment for specific disorders, where to obtain treatment, and how to pay for it. Requests for referrals to specialists and medical centers were received constantly. Information about drugs--especially "orphan" drugs and the Institute's role in their development--was also anxiously sought by patients whose conditions do not respond to available drug therapies.

This year, 478 individually prepared responses were sent to the Institute's lay and medical audiences. Another 161 responses were written in answer to controlled letters from the Congress and the White House. Also, 118,710 inquiries were answered with publications; 1,440 of these were accompanied by form responses or personal notes providing additional information. Another 137,456 publications were sent out to fill bulk requests from voluntary health agencies, medical centers, and local and state agencies. Still another 6,453 publications were distributed to scientists and physicians at medical meetings.

During this reporting period there was a dramatic decrease in publications supplied to voluntary health agencies--the direct result of the printing moratorium which prevents OSHR from reprinting publications, thereby forcing the Office to conserve limited supplies. At the same time, the number of publications sent to individuals increased, largely due to media interest in several new Hope Through Research pamphlets. This change in distribution considerably increased the workload of the Public Inquiries Section: handling 500 individual requests requires far more effort than shipping a bulk order of 500 publications to a single address.

Public Inquiries Section personnel also plan and develop the NINCDS exhibits program, and serve as Institute spokespersons at the medical and scientific meetings to which the various exhibits are sent. Last year, the Section staff worked with NIH Medical Arts on the design of 5 new picture panels for the NINCDS exhibit. The full-color panels depicted otolaryngological research, PETT, and basic research activities. The addition of the new panels to the exhibit increased its overall flexibility and adaptability to specific audiences important to Institute programs.

Plans to develop an exhibit specifically for neurosurgical meetings were delayed by budgetary considerations and the Institute's decision to cut back temporarily on the number of meetings to which the exhibit is sent. However, new panels are being designed for meetings attended in support of the Communicative Disorders Program.

In the fall of 1981, the NINCDS exhibit was shown at meetings of the Child Neurology Society in Minneapolis, and the Society for Neuroscience and the American Speech, Language and Hearing Association, both in Los Angeles. From January through September 1981, the exhibit was sent to meetings of the Association for Research on Otolaryngology in St. Petersburg; the American Academy of Neurology and the American Neurological Association, both in Washington, D.C.; the Triological Society in Palm Beach; the Biophysical Society in Boston; the American Association of Anatomists in Indianapolis; the Association for Chemoreception Sciences in Sarasota; and FASEB in New Orleans. The last four of the above meetings were scheduled in response to the Institute program directors' desire to interest specific scientific audiences in applying to NINCDS for research support.

As one way of carrying out the Institute's commitment to encouraging minority scientists to undertake biomedical research, the OSHR in cooperation with the NINCDS EEO Office sent exhibits to the Minority Biomedical Support meeting in Albuquerque and the National Medical Association meeting in San Francisco.

The Public Inquiries Section also carries out a small initiative to meet the special information needs of NINCDS employees. The chief vehicles for conveying information via office bulletin boards is NINCDS CLIPS, a poster-sized sheet of news clippings about the Institute. CLIPS and other materials are distributed frequently to inform employees of research accomplishments of NINCDS scientists and grantees, to advise them of policy changes, and to alert them to radio and TV coverage of NINCDS work.

Similarly, news reaches internal audiences through the NIH RECORD, which this year carried more than two dozen news and feature stories prepared by OSHR writers. A number of these stories prompted media inquiries or were picked up by other publications for further dissemination.

The Public Inquiries Section also continued this year to provide materials for the Institute's Advisory Council meetings, and has updated the Council Directory.

The head of the Section also serves as information liaison with the Extramural Activities Program and with the program directors in the Federal Building; she is responsible for identifying grantee research that is appropriate for use in Institute reports and publications, and writes annual special reports for Congress on cerebral palsy and spinal cord injury.

This year, Institute responsibilities under the Freedom of Information Act, formerly centered in the Public Inquiries Section, were transferred to the Office of Grants Management.

Scientific Publications Section

The Scientific Publications Section produces and distributes Institute publications for a variety of scientific and professional audiences and for the general public. The Section serves all the administrative units of the Institute, ad hoc committees preparing reports, and, as appropriate, outside organizations working in the neurosciences. The services cover planning,

clearance, writing, and editing of publications; securing designs, layouts, and printing; distributing and storing publications; and subsequent revision and reprinting according to demand.

A priority project of the Publications Section has been revising and expanding the Institute's Hope Through Research pamphlet series. These pamphlets offer information of interest and value to patients and their families, and describe research approaches to the various neurological and communicative disorders. During this fiscal year, new pamphlets on epilepsy, shingles, brain tumors, hearing loss, and chronic pain were published. Work began on new pamphlets on stroke, Parkinson's disease, and head injury, but publication was delayed because DHHS approval for these projects was not granted until August 1982.

NINCDS fact sheets are another series of publications the Section has developed to meet a need for information about rare and little known neurological and communicative disorders. Thirteen fact sheets are now in print. This year, a revised fact sheet on Friedreich's ataxia was published, as well as a new fact sheet on torsion dystonia. A fact sheet on Joseph's disease was prepared for possible publication in FY83.

NINCDS Extramural Research and Training Awards, a guide for grant applicants, was revised and published this fiscal year. NINCDS Intramural Research Training Programs, describing training opportunities within the Institute's laboratories and research branches, was also revised and published. The design of these two publications resembles that of The NINCDS Today and the NINCDS Fact Book, so the four publications, none more than a year old, can be recognized as a "family" with the common purpose of describing the Institute and its programs.

The NINCDS Today, a 20-page, four-color booklet describing and depicting the work of the Institute, was published and distributed in FY82. This publication won a first place in the Blue Pencil Awards contest sponsored by the National Association of Government Communicators, and was also selected by the Art Director's Club of Metropolitan Washington for display in their annual show.

A service performed by the Section has been production of guides for health practitioners, presenting the latest information in research and treatment of various disorders. In FY82, the Section published Epilepsy: A Manual for Health Workers, written originally for physicians and paramedical personnel in third world countries but adapted by the Section for worldwide use. This manual was given international distribution.

NINCDS's Office of Biometry and Field Studies operates a long-term program of hospital studies to produce authoritative statistics on incidence, prevalence, and costs of the major neurological and communicative disorders. A by-product of this program is a series of short brochures presenting highlights of study results. The second publication in this series, National Head and Spinal Cord Injury Survey, was published and distributed in FY82.

The NINCDS Fact Book, updated to July 1981, was produced and distributed. Late in the fiscal year, a third edition of this publication was prepared and readied for printing.

Two useful directories were updated but because of the moratorium were not published: Voluntary Agencies Working to Combat Neurological and Communicative Disorders and NINCDS Directory of Professional Societies.

Two periodical issuances, not publications but essential to the OSHR communication mission, are NINCDS NOTES, a monthly Institute news service to journal editors, and RESEARCH CURRENTS, a triannual packet of lay-language science articles which now goes to some 100 voluntary agencies sharing interests with NINCDS. Response to RESEARCH CURRENTS has been favorable, with many of the articles reprinted in voluntary agency newsletters.

During 1982, a summer intern assigned to the NINCDS Equal Employment Opportunity Office and working under the supervision of OSHR produced the first issue of NINCDS EEO/Personnel News Briefs, an information page designed to inform employees about important Personnel and EEO issues. News Briefs may be issued periodically as needed.

Media Liaison

NINCDS research on neurological and communicative disorders continues to attract media attention, with certain areas the focus of more than usual interest. Among research topics that most intrigue reporters are the dementias, brain imaging technology, and spinal cord regeneration. The OSHR deputy chief, who has primary responsibility for media liaison, responds to inquiries but also seeks to develop interest in areas that are crucial to the Institute's mission.

Among the OSHR media activities reaching national audiences this year was the radio program "Prime Time," which chose to feature an NINCDS scientist in its show on Alzheimer's disease. Hundreds of letters were received from listeners as a result of the show, which was broadcast nationally several times. Similarly, NINCDS research was frequently spotlighted on the local CBS television affiliate in brief health reports that were sometimes picked up nationally.

Print reporters regularly turn to OSHR for information on diverse topics. This year a major piece on the role of voluntary health organizations in combating neurological and communicative disorders appeared in the LOS ANGELES TIMES as a result of a story idea placed by the OSHR deputy chief. Similarly, on OSHR's recommendation columns about research on shingles and stuttering appeared in the WASHINGTON POST and the NEW YORK TIMES, producing thousands of requests for new Hope Through Research pamphlets on these subjects.

Often a single research finding will be of interest to a variety of media if presented in an intriguing fashion. This year, for example, OSHR helped disseminate to the public findings concerning the ineffectiveness of the TORCH test commonly used by obstetricians and gynecologists. Through the intervention of OSHR staff, stories recommending that physicians not use

the TORCH test appeared in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, WOMAN'S DAY, NIH RECORD, NEWS & FEATURES, RESEARCH CURRENTS, and locally on WDVM-TV. It is impossible to know how many other media outlets used this information after seeing the story in one of these publications or on television.

OSHR also assisted with an NIH science writers' seminar on slow virus research, with major stories about this research appearing in SCIENCE NEWS, NEW YORK TIMES, U.S. MEDICINE, and other national newspapers and journals. The results of a consensus development conference on CT scanning of the brain were also disseminated widely through OSHR media liaison efforts.

The Media Liaison Section is expanding efforts to provide information about NINCDS activities to professional societies concerned with the neurosciences. Initial efforts are being made with professional groups interested in communicative disorders, with the primary goal of mounting a cooperative national campaign to inform the public about the problem of presbycusis.

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Office of Planning and Analysis
Office of the Chief
National Institute of Neurological and Communicative Disorders and Stroke

The Office of Planning and Analysis (OPA) advises the Institute Director and Office of the Director (OD) staff as well as components of the intramural and extramural programs of the Institute on a wide variety of programmatic issues and requirements. These include program development, analysis, evaluation, the development of implementation plans, legislation, and data coordination. The OPA provides staff support to facilitate the integration of program planning, analysis, and evaluation efforts in the categorical program areas. It also provides the Director and the Executive Staff with assistance in coordinating the development of research plans for meeting these goals.

The OPA develops, in collaboration with Program Managers and Directors, the Institute responses on a number of issues, including analyses of specific aspects of research programs. Staff serve in a liaison capacity for reporting research on various subjects. An analysis of NINCDS prevention activities involved identification of the total Institute research matrix to extract FY 81 projects related to primary, secondary, and tertiary prevention. Data is also coordinated and compiled regarding NINCDS clinical trials activities as well as activities related to technology assessments and consensus conferences.

The OPA this year initiated a series of meetings with the Program Directors and other key Institute personnel to assess the past and current role of the office and to elicit suggestions and reactions to a variety of initiatives planned for the future. Following these meetings, recommendations regarding potential future initiatives were made to the Acting Director. One such recommendation resulted in the OPA initiating a comprehensive review and analysis of the NINCDS legislative charter as well as the legislative charters and histories of several other NIH Institutes. On June 21, 1982, a meeting of key OD staff as well as two former NINCDS Directors was convened for the purpose of discussing relevant legislative issues. Work is now in progress to implement the recommendations developed at that meeting.

Analysis and Reports Section (ARS)

The Section prepares and coordinates the annual Evaluation Plan for the research programs of the Institute and develops proposals for the recurrent assessment of the effectiveness of its research programs. This year the Section conducted an information session for all interested Institute staff on the procedures and requirements for obtaining one percent set-aside evaluation funds. The FY 83 NINCDS Evaluation Plan contains five proposals. Included among these is a proposed project to develop research goals for the neurological and communicative sciences. This project will build upon the previously developed National Research Strategy. Section staff also serve as evaluation contacts and Institute representatives in all activities

related to evaluation. The Section provides to NIH material requested by the Assistant Secretary for Planning and Evaluation regarding the status of ongoing evaluation projects and utilization and application of their findings.

The Section prepares and coordinates the development of the Research and Legislative Plan of the Institute. This plan is concerned with setting the major themes, thrusts, and tone for the discussion of budgetary requirements for future years. Input is also solicited and obtained from the Program Directors and from the Director and Deputy Director of NINCDS. Budgetary projections are developed by the Budget Office in close collaboration with the Section. Questions raised by NIH/OD are responded to jointly by the Budget Office and the Section.

The ARS also has the responsibility of coordinating development of the Institute Annual Report. The Section works with the Institute's Program Areas and provides them with technical assistance to assure uniformity of format and editorial quality of the Report. The Annual Report is a standard formal Institute document which presents an overview of the total scope of NINCDS research as to science, program, and budget. Program summaries as well as contract narratives and intramural research project summaries are included.

As a legislative focus for the Institute, we have continued to work with appropriate staff of NIH/OD to monitor legislative developments in order to safeguard and maintain all elements of the Institute's mission. Legislative proposals pertaining to NIH reauthorization, neurofibromatosis, government-industry cooperation, orphan drugs, and other areas of vital interest to NINCDS were reviewed and recommendations were forwarded to the Office of the Director.

The Section also participated in the development and review of the annual Implementation Plan of the Institute. This involves setting funding priorities within the context of program objectives, research opportunities, and available resources. This is done in close collaboration with the NINCDS Office of the Director.

The ARS also responds to a large number of ad hoc queries from a variety of private and public sources regarding NINCDS research as it relates to NHLBI, NIEHS, pain research, research on the handicapped, toxicology, aging, and a variety of other important areas. In addition the Section provides NINCDS representation on Interagency Technology Committees such as Digestive Diseases, Dermatology, and Arthritis.

Information Technology Section (ITS)

This Section has been responsible for developing a Program Information System (PINS) to combine programmatic, fiscal, and management data into an integrated Institute-wide database. Validation of programs and assistance has been provided by the firm of JRB Associates, Inc. Considerable ITS staff effort during the first nine months of the year was directed to the continuing development of the System. While significant progress was made, the scope and complexity of the PINS

effort led to the view that it was beyond the resources of the Institute. Therefore, PINS was terminated by the Acting Director, NINCDS, on June 24, 1983.

A concurrent effort that was concluded in mid-year was the development of an interactive system for the storage and retrieval of drug reaction data for both inpatients and outpatients participating in clinical trials. This system was turned over to the Intramural Research Program for operation. The Section served as the focal point within the Institute for ADP coordination, preparation of the annual ADP plan, and related activities. Due to PINS termination, ITS was abolished in July 1982, and its personnel were reassigned to other positions as appropriate.

On September 1, the Office of Data Analysis and Reports, Extramural Activities Program, was abolished, and its personnel were reassigned to the newly created Management Information and Data Section, OPA. The new Section has the responsibility for administering the Institute information and data system which involves the collection, classification, organization, storage, and retrieval of data for research grants, training grants, career awards, fellowships, contracts, and intramural research projects. It will produce special and recurring reports and other computer-prepared documents to meet Institute and Institute Program needs as well as developing and implementing automated processes to facilitate reporting as it affects program administration.

CONTRACT NARRATIVE
Office of Planning and Analysis, OD/NINCDS
Fiscal Year 1982

Contractor: JRB ASSOCIATES, INC., 8400 Westpark Drive, McLean, Virginia 22101 (NO1-NS-82301)

Title: Validation and Technical Support -- NINCDS Program Information System

Date Contract Initiated: November 1, 1981

Contractor's Project Director: Jacqueline Sanders

Current Annual Level: $17,000

Objectives: The contractor was expected to continue providing technical support to the Institute by refining the program which updates the PINS database from IMPAC, developing a program to copy ODAR classification codes from IMPAC, revamping and installing an audit trail to record changes to data in the files, and refining classification data entry and modification programs to facilitate processing by ITS support staff. Completion of an interface with the NIH organization file and data entry of intramural research projects were also required. It also was to lay the groundwork for ITS to complete the creation of an FY '81 frozen file through file definition and coordination of online usage and development of the History Maintenance Program.

Major Findings: Considerable effort was aimed at producing a working file that could demonstrate both the usefulness and the report capability of PINS. A file was loaded with IMPAC data and efforts were directed to an audit trail for recording changes to data within the files. Several programs for reports were made operational. ITS programming staff was aided in debugging problem programs and several training sessions took place concerning the database administration of the system.

Significance to the Program of the Institute: The scientific, budget, and program information of the Institute is increasing in quantity and complexity. Rapid access to pertinent facts in a timely manner is essential for effective management. PINS is being developed as a database management system providing online access to the data by organizational units throughout the Institute. Data will be accessible when and where they are needed and in a form that can be readily used. PINS will maintain data currency, validity, and compatibility between it and existing NIH systems such as IMPAC.

Proposed Course: The contract terminated on December 19, 1981.

TAB 1.A -- OFFICE OF BIOMETRY & FIELD STUDIES -- OBFS/OD

ANNUAL REPORT
October 1, 1981 through September 30, 1982

Office of Biometry and Field Studies
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Table of Contents (cont'd)

Table of Contents (cont'd)

Table of Contents (cont'd)

Annual Report
for period October 1, 1981 through September 30, 1982
Office of Biometry and Field Studies
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

The Office of Biometry and Field Studies (OBFS) supports a program in biostatistics and computer science to further medical research in the areas of neurology and communicative disorders.

OBFS is active in a number of program areas, such as computerized clinical data banks, national surveys of disease, and there has also been a considerable increase in the Branch's clinical trial activities, both intramurally and in consultation with university-affiliated groups that conduct clinical research.

A major OBFS responsibility is management of the NINCDS Stroke and Traumatic Coma Clinical Data Banks. The Stroke Clinical Data Bank is a cooperative, prospective study of hospitalized stroke patients, which is now moving into its main five-year phase. In the pilot project, data on over 1100 cases were collected at four clinical centers. Among the studies drawn from these data is one relating post-stroke depression to location of brain injury. This work found that among right-handed persons with ischemic infarctions, those with lesions of the left hemisphere were more likely to be depressed than those with lesions of the right hemisphere or with brain stem injury. Inappropriate mood and depth of depression were also shown to be associated with location of injury.

Another study has examined the clinical features and patient characteristics associated with development of post-stroke complications. Preliminary findings suggest that risk of complications is associated with age, sex, race, severity and laterality of stroke, functional ability, and stroke type. Further analysis will provide a profile of the complication-prone patient.

A third study has focused on patients with lacunar infarcts. The object of this study, among the 100 patients found with lacunar stroke, is to delineate subtypes, and determine the clinical outlook and risk factors for each subtype. Histories of hypertension or diabetes were found more frequently among these patients. Preliminary analyses indicate that functional prognosis and survival are better for lacunar infarctions than for other stroke types.

Stroke Data Bank research includes the development of a new diagnostic algorithm for stroke, and its use as a prognostic index, by studying its relationship to laboratory evidence and to activities of daily living. In addition, work has begun on refining the data collection forms and protocols from the pilot for use in the main phase of the Stroke Data Bank.

The Traumatic Coma Clinical Data Bank, which is also moving into a five-year main phase, is a collaborative effort involving five neurosurgical departments and OBFS. From January 1980 through March of 1982, the pilot project prospectively collected information on over 680 comatose hospitzlized accident victims. These data have undergone extensive quality assurance reviews and are presently being analyzed for research findings. Studies in progress include an investigation of the relationships among accident characteristics, injury

details, emergency care and outcome, and a study of patients with subdural hematomas.

A study of patients whose initial post-injury condition appears not to be serious but who swiftly deteriorate, has identified about 40 such cases from the first 325 cases in the data bank. Analysis of data from these 40 cases has shown an association between computerized tomographic findings of midline shift and poor prognosis. Another study drawn from the 681 cases in the coma data bank examined the relationships among pre-hospitalization hypotension and hypoxia, elevated intracranial pressure and outcome. Each of these secondary insults was shown to be associated with outcome.

OBFS personnel have provided consultation on data bank design and implementation to scientists at NIH and elsewhere. OBFS is assisting in the planning of a Workshop on Computers in Neurology for the 1983 American Academy of Neurology meeting, and will give a presentation on clinical data banks. OBFS is also developing a workshop to be held in conjunction with the 1983 Stroke Council meeting of the American Heart Association to report to the neurological community on the methodology and findings of the Stroke Clinical Data Bank.

The data entry, data transmission and report generating system of the microcomputer used in the Stroke and Coma Data Banks has been substantially improved in FY 1982. One part of this computer system creates a narrative case summary for individual patients. A method for electronically transferring data sets overnight without a computer operator's assistance has been developed. This is an innovative step in data management for clinical data banks and for other types of multicentered studies.

Another major program initiative is clinical trial research. OBFS is the statistical coordinating center for several continuing or planned clinical trials. With the Developmental Neurology Branch, NDP, it has established the statistical coordinating center for a clinical trial that addresses the issue of the potential loss of cognitive function in children who have febrile seizures and are treated with phenobarbital.

OBFS participated in the design of a clinical trial on the efficacy of spinal manipulative therapy as a treatment for musculo-skeletal dysfunction on the performance of athletes, in collaboration with the Acting Director, NINCDS, and Yale University.

OBFS has been actively consulting on a number of proposed clinical trials. The most active area for potential clinical trials is for new therapies for multiple sclerosis. OBFS has provided consultation and statistical guidance to investigators at Albert Einstein Medical College in developing clinical trials for COPOLYMER I. Pilot studies suggest that COPOLYMER I benefits both exacerbating-remitting and chronic progressive multiple sclerosis.

OBFS has provided statistical consultation for other clinical trials of therapy for multiple sclerosis, including plasmapheresis at Childrens Hospital in Boston, and methylprednisolone and azathioprine at UCLA. There will be an OBFS representative on the Safety Monitoring Committees of the COPOLYMER I and the plasmapheresis trials.

In anticipation of further collaboration in clinical trials, for which OBFS would provide data management, project coordination, computer support and statistical analysis, OBFS has planned an external operations center to support the OBFS statisticians in these collaborative projects.

In addition, an innovative computer and data management system has been developed by OBFS staff. This system utilizes the Hewlett-Packard minicomputer at OBFS as well as the DCRT computers, for checking eligibility of patients for entering a trial, registering them and randomly allocating patients to treatments. The system improves the efficiency of data entry and management, ascertainment of patient status, data tracking and the production of charts, tables and reports on the progress of the trial. Current OBFS activity on the system includes enhancements in the area of quality assurance and simplifying transmission of data from the OBFS mini-computer to DCRT for access to extensive statistical software. The system currently provides support for a study of Medline usage funded by the Communicative Disorders Program (CDP) of NINCDS, and for the trial of barbiturate therapy and cognitive changes in children.

Pain is the focus of a number of investigations which are under way. OBFS has initiated a meeting of pain experts to determine whether there has been sufficient progress in the methodology for the assessment and measurement of pain to warrant the sponsorship and organization of a symposium on that subject. The Intramural Program and all of the Extramural programs of NINCDS are collaborating with OBFS in planning and funding this meeting.

OBFS prepared a report based on an investigation of sensory decision theory measures for deriving psychophysical measurements of pain. A study of the statistical characteristics of the temporal patterns of persistent, episodic pain such as migraine headache is currently being developed.

In collaboration with the Office of Analysis and Epidemiology, NCHS, OBFS is evaluating the average and age-specific incidence rates of various chronic pain syndromes, and investigating their association with epidemiologic factors. For example, the relationship between incidence and prevalence rates and length of illness due to headache has been examined, and a report has been prepared. A study is currently being developed to evaluate the age-specific incidence of neck-back pain and low back pain and their association with demographic, psychological and medical care variables based on NCHS national surveys.

In collaboration with the Developmental Neurology Branch, NDP, an investigation is under way to measure the relationship between migraine headache and pregnancy, based on Perinatal Project data. Preliminary results indicate that children of mothers with a history of migraine have a higher incidence of seizures than do children of mothers free of migraine.

As a major initiative in the area of pain, the OBFS is engaged in a study of severe and debilitating headache. The principal objectives of the study are to (1) investigate risk and etiological factors associated with headache; (2) develop classifications of headache; and (3) describe the magnitude and extent of the headache problem in a geographically defined population. The survey will be based upon telephone interviews of adults from a random sampling of households located within the geographic area of study. In preparation for an

area survey of this disorder, a questionnaire, procedures for telephone interviewing, and an operational classification of headache have been developed. Several headache clinics are collaborating with OBFS in this effort. These clinics have provided abstracts of the medical records of 400 clinic patients; these patients are participating in telephone interviews about their headache experience. Information elicited during the interviews will be compared with that found in the abstracts.

Data from the National Multiple Sclerosis Survey indicate that as of January 1, 1976, there were 123,000 reported cases of multiple sclerosis in the conterminous United States (a rate of 58 per 100,000 inhabitants). The annual incidence for the period 1970-1975 was estimated to be 8,800 (a rate of 4.2 per 100,000 inhabitants). Professor Robert P. Inman of the Wharton School examined the consumption losses due to the disease. The estimated annual cost per patient, for 1976, was $6,527 or $800 million for all the reported cases. An examination of the mobility data revealed that slightly over 50 percent of the patients reported difficulty getting around indoors and outdoors, but 40 percent reported no mobility problems. Nearing completion is an analysis of data on the psychosocial factors that affect employment. This multiple sclerosis study is being performed in collaboration with investigators from Albert Einstein College of Medicine. Additionally, a brochure highlighting the findings of the survey is being prepared, in cooperation with Dr. Emanuel Stadlan of NDP.

A report on the findings from the National Survey of Intracranial Neoplasms is under review by the Stroke and Trauma Program and will be submitted for publication.

An epidemiologic study of stroke incidence in three counties in southern Alabama has been completed. The age-adjusted incidence rate for blacks was almost twice that of whites. Two-thirds of the stroke cases had a history of hypertension and one in five had a history of diabetes.

A study to test a three-step case-finding strategy for a national survey of epilepsy has been completed. First, prescriptions for anticonvulsant drugs were sampled at pharmacies. Second, physicians who wrote the prescriptions were asked about the diagnoses of patients whose prescriptions had been selected for study. Third, some of the patients considered to be epileptic by the physicians were interviewed briefly to find out about the number of different anticonvulsant drugs taken and where the drugs were obtained. From preliminary information, it appears that this case-finding strategy will have to be modified for use in a national survey since the combined nonresponse rate (pharmacies, physicians, patients) was high. A final report on the study is forthcoming.

A feasibility study of the Hospital Discharge Survey to develop a system for the periodic collection of morbidity and clinical data from hospital records has been completed. This study was conducted in collaboration with the National Center for Health Statistics (NCHS). The study developed 15 clinical algorithms for use in case ascertainment and classification for disorders of interest to NINCDS, NHBLI, NCI, and NEI. The yield of acceptable cases from the pertinent ICDA codes and the methodology for estimating the incidence and prevalence of these disorders from the information were determined. The

results show that this methodology could be used for a system of collecting periodic national data to study trends in neurologic disease rates.

The Copiah County Study, a joint effort of the OBFS, the United States Bureau of the Census, and the University of Mississippi Medical Center, has been completed. The study generated prevalence estimates for major neurological disorders in the biracial population of Copiah County, Mississippi. A report has been published on the methodology of the study. Another is expected to be the first published report on the prevalence of essential tremor for a geographically defined population within the United States. Two other reports, one on cerebral palsy, the other on stroke, are in preparation this year.

The Senile Dementia Study is a collaborative effort of the OBFS, the National Institute of Mental Health, and the Johns Hopkins University. It is currently in the second phase of data collection, which involves reinterviewing the cases approximately one year after their initial interview, to note changes in their condition over the interval. During the first phase, 39 cases of senile dementia were identified, given neurological examinations, and interviewed. A control group was also interviewed.

The OBFS is working with the Division of Heart and Vascular Diseases, NHLBI, in analyzing hearing data collected during Cycle 15 of the Framingham Heart Study. The main objectives of this investigation are to (1) describe the prevalence of hearing impairment in the Framingham cohort, by demographic characteristics; (2) investigate the relationship between the severity of hearing impairment and risk factors for hearing loss, such as noise exposure and toxicity and (3) investigate possible relationships between hearing impairment and cardiovascular risk factors and outcomes.

A study of the incidence and prevalence of multiple sclerosis in two Colorado counties is in progress. This study involves researchers from OBFS and the Rocky Mountain Multiple Sclerosis Center in Denver. Colorado is suspected of having a higher prevalence of multiple sclerosis than would be expected, given the State's latitude. If the hypothesis of a higher prevalence is borne out, then additional studies will be undertaken to seek possible explanations.

The OBFS has launched an effort to publish a series of disease-specific reports on neurological disorders. These reports will include data on the incidence, prevalence, and mortality of the disorders, as well as recommendations for additional studies that need to be done. An investigator from the University of Maryland is preparing the first report on Parkinson's Disease.

A significant effort continues to be focused on the analysis of data from the Collaborative Perinatal Project. Intensive studies are proceeding in the areas of febrile seizures, neonatal seizures, convulsive disorders, cerebral palsy, and maternal infection during pregnancy.

A multi-stage program is progressing to determine the optimal management of children with febrile seizures. The consensus meeting held in 1980 delineated several areas of needed research including (1) the usefulness of the EEG in predicting later recurrence of seizures in children with a febrile seizure

and (2) the possible harmful side effects on cognitive function of administration of chronic phenobarbital to children with febrile seizures. In collaboration with the Developmental Neurology Branch, NDP, OBFS has initiated two major research studies to answer these questions: (1) the clinical trial of phenobarbital and (2) the Yugoslavian study of the predictive value of the EEG in febrile seizures. In collaboration with the Neurological Disorders Program and the American Medical Association, OBFS has engaged in a physicians' survey of practice in the management of children with febrile seizures, a study which also provides information regarding these questions.

A collaborative investigation of head injury was designed with OBFS and the Departments of Neurosurgery at the University of Virginia and at the All-India Institute of Medical Science in New Delhi. The proposal has been approved by the Government of India. It has been funded for three years with PL480 rupees. The proposal will now enter the NIH peer review process. If approved, the pilot phase will be a comparative study of the two head-injured cohorts; the second phase will include clinical trials of therapy for head-injured patients.

OBFS has initiated the development of a consortium of center grant and individual investigator grant proposals whose primary objective will be studies of the neurological aspects of aging in Macaca mulatta primates. In collaboration with NDP and the Grants Management Branch, OBFS is working with the proposed grantees, the University of Puerto Rico, the Veterans Administration Hospital in San Juan, and Dr. Donald Price and his colleagues at the Johns Hopkins University, to generate a number of study proposals whose unifying characteristic is the use of aging primates at the under-utilized Caribbean Primate Research Center. The OBFS contribution will include the provision of a statistical coordinating and data operations center for all of the study data which are developed from the primate studies. A major objective of OBFS would be to explore the association of data items across individual study boundaries. For example, it might be fruitful to determine the association, if any, between primate behavioral characteristics of aging as identified by the behavioral group at the University of Puerto Rico, and pathological neurotransmitter findings of Dr. Price and his associates. The Division of Research Resources (DRR) is helping to identify DRR funded sources of aged primates which might be secured and added to the present primate colony in Puerto Rico.

Intramural Program research collaboration continues to be an important element of OBFS activities, and OBFS investigators participate fully in all phases of the projects in which they are involved. The range and variety of problems utilize the varied talents of the OBFS staff which, in addition to mathematical statistics, include those of mathematics, epidemiology, demography, survey statistics, physics and computer science. The latter two, for example, are extensively relied upon for the work in computer-aided tomography.

There are 15 projects in which OBFS is currently collaborating with scientists in the Intramural Research Program. They include a wide range of subjects, such as methods for enhancement of computer-aided tomography, assessment of regimens for Parkinson's disease, assessment of the potential teratogenic effect of phenytoin and valproic acid, and the role of antiviral antibodies in multiple sclerosis.

In the area of clinical trials, OBFS has collaborated with the Experimental Therapeutics Branch (IRP) on clinical studies of Parkinson's disease. Both in-patient and out-patient clinical trials of new drugs or the new application of standard drugs (e.g., lisuride, bromocriptine, pergolide) have been initiated with Parkinson's disease patients. OBFS has been involved in the design and analysis of these trials as well as in the monitoring of the accumulating data and the analysis of adverse reactions.

Collaborative work with the Infectious Diseases Branch includes the development of methods to account for variation for bioassay techniques, and the determination of the role of viruses in multiple sclerosis. The latter activity includes case-control studies and a study of twins.

A study of cognitive, psychological, and clinical differences in twins, discordant with respect to Parkinson's disease, is nearing completion. This project is in the Section on Neuroepidemiology, with the Experimental Therapeutics Branch providing clinical evaluations, and OBFS is providing the statistical analysis of the data.

OBFS statisticians have also been active in the research and development of statistical methods and theories to meet the needs of NINCDS in design of experiments, analysis of data, and statistical modeling of biological processes and phenomena. Current studies include methods of nonparametric regression, determination of sample sizes for clinical trials with multinomial outcomes, regression in Poisson data, sequential methods with early stopping, two-period cross-over designs for Phase II clinical trials, regression methods for survival data, patient recruitment monitoring, ranking and selection methods, case-control studies with unequal number of controls per case, and Markov modeling of clinical features of Parkinson's disease.

OBFS maintains and fosters an active interest within NIH and elsewhere in methodological issues in the application of statistics and computer science to medicine. The Branch actively participates in the American Statistical Associaion, the Biometric Society and the Association for Computing Machinery with staff holding offices, acting as reviewers for the journals, organizing sessions at meetings, making presentations at meetings, and publishing papers. Two members of OBFS became Fellows of the American Statistical Association in 1982.

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OFFICE OF BIOMETRY & FIELD STUDIES
Section on Mathematical Statistics

Consultation with IRP

Dr. John Barranger, Developmental and Metabolic Neurology Branch: Copper absorption in Menke's Disease.

Dr. Christopher Ward, Experimental Therapeutics Branch: Study of Parkinson's Disease in Twins and Study of Objective Measurements of Movement Disorders.

Dr. Rodney Brooks, Neuroradiology and Computed Tomography Section: Surgical Neurology Branch, Enhancement of CAT and PET scanning techniques and optimization of PET Scanner Software.

Dr. John L. Sever, Infectious Diseases Branch: Study of Toxoplasmosis in pregnant women, study of relation of serological infection during pregnancy to outcome in children.

Dr. Roswell Eldridge, Section on Neuroepidemiology: Parkinson Twin Studies.

Dr. George H. Weiss, Physical Sciences Laboratory, DCRT, the Use of Phantom Views to Diminish an Artifact in CT Scans.

Dr. William B. Marks, Intramural Research Program, NINCDS: Statistical analysis methods in neuronal spike data.

Dr. William T. London, Infectious Diseases Branch, IR, Estimation of Sample Sizes for Testing Positive Antibody Titers in Macacas on Cayo Santiago.

Dr. Lata Nerurkar, Infectious Diseases Branch, IR, Comparison of ELISA and IHA methods for detecting infection.

Dr. Anita Chu, Infectious Diseases Branch, IR, Reye's Syndrome Study.

Dr. Elizabeth Barbehenn, Laboratory of Neural Control, Study of Frog Retina.

Dr. Isabel Shekarchi, Infectious Diseases Branch, Evaluation of the ELISA method of bioassay.

Dr. Christy Ludlow, Communicative Disorders Program, Jitter as a function of fundamental frequency and other factors.

Dr. Joanna Woyciechowska, Infectious Diseases Branch, IR, Antiviral antibodies in Multiple Sclerosis.

Dr. Peter LeWitt, Experimental Therapeutics Branch, Clinical Trial of Pergolide and Bromocriptine in Parkinson's Disease.

Dr. William London, Infectious Diseases Branch, IR, Allometric Relationships in Four Species of Primates.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1982

1. Univ. of Maryland (NO1-NS-2-2302)

2. Univ. of S. Ala. (NO1-NS-2-2397)

3. Boston Univ. (NO1-NS-2-2398)

4. Michael Reese Hospital & Medical Center (NO1-NS-2-2399)

Title: Full Phase Stroke Data Bank

Contractor's Principal Investigators:
1. Dr. Thomas Price
2. Dr. Jay Mohr
3. Dr. Philip Wolf
4. Dr. Louis Caplan

Current Annual Level FY'82:
1. $185,097
2. $186,578
3. $174,029
4. $168,467

Objectives: The primary objective of this project is to implement a full phase computerized interactive data bank network which will contain uniform longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which collect data, a data base management center to store and manipulate the data and staff at OBFS who have the responsibility for data analysis.

Major Findings: This project will benefit from the experience gained in the Pilot Data Bank Network in Stroke, which produced a uniform vocabulary of data elements including diagnostic sub-classifications of Stroke, test results, medical and surgical therapy, complications, and measures of stroke deficit and recovery.

Significance to the NINCDS Programs and Biomedical Research: The Full Phase Stroke Data Bank Network is important because it will provide a resource of high quality data on the clinical course of stroke. The project serves as a prototype for national data bank networks for other neurological disorders.

Proposed Course of the Project: This is the first year of a five year project. The initial course will include determination of research questions to be investigated, and design of forms to collect the data. The experience of the Pilot Data Bank Network in Stroke will be very useful to the Full Phase Project, but the investigators will also be innovative in their approach to the best research use of the system.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1982

1. Univ. of Maryland (N01-NS-9-2302)

2. Univ. of S. Ala. (N01-NS-8-2397)

3. Duke Univ. (N01-NS-8-2396)

4. Boston Univ. (N01-NS-8-2398)

Title: Pilot Data Bank Network in Stroke

Contractors' Principal Investigators:

1. Dr. Thomas Price
2. Dr. Jay Mohr
3. Dr. Albert Heyman
4. Dr. Philip Wolf

Current Annual Level FY'82:

1. $ 7,500
2. no cost
3. no cost
4. no cost

Objectives: The primary objective of this project is to develop a computerized interactive data bank network which will contain uniform, longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which collect data, a data base management center to store and manipulate the data and staff at OBFS who have the responsibility for data analysis. This project has met its objectives and will continue into a full-phase with competitive awards.

Major Findings: This project has produced a uniform vocabulary of data elements including test results, medical and surgical therapy, complications, and measures of stroke deficit and recovery. The collaborating hospital centers have collected data on approximately 1,000 stroke patients.

Significance to the NINCDS Program and Biomedical Research: The Pilot Data Bank Network in Stroke is important because it demonstrated the feasibility and utility of having medical centers collaborate to provide a resource of high quality data on the clinical course of stroke. This project will serve as a prototype for a national data bank network for other neurological disorders.

Proposed Course of the Project: This project has achieved its primary objectives and have been completed. Currently manuscripts describing the data bank and its findings are being prepared for publication.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

1. Univ. of Texas-Galveston and Baylor Univ. Medical College (NO1-NS-9-2308)

2. Univ. of Cal. in San Diego (NO1-NS-9-2309)

3. Medical College of Virginia (NO1-NS-9-2307)

4. Univ. of Virginia (NO1-NS-9-2306)

Title: Pilot Data Bank Network in Traumatic Coma

Contractors' Principal Investigators

1. Dr. Howard Eisenberg
2. Dr. Lawrence Marshall
3. Dr. Donald Becker
4. Dr. John Jane
5. Dr. Robert Grossman
6. Dr. Kamran Tabaddor

Current Annual Level FY'82

1. $52,000
2. 43,376
3. 41,000
4. 33,000

Objectives: The primary objective of this project is to develop a computerized interactive data bank network for traumatic coma patients. This data bank will be used for clinical research and patient management.

Major Findings: This data bank project has developed and is utilizing a uniform vocabulary to collect patient data which will include the details of the accidents, test results, therapies and outcomes. The Glasgow Coma Scale is part of this vocabulary. Data from 681 severely head injured patients were collected from January 1980 to February 1982 and data analysis is continuing.

Significance to the NINCDS Program and Biomedical Research: The Traumatic Coma Data Bank Project is important for several reasons. Longitudinal data on severely head injured traumatic coma victims were collected at six centers using uniform definition and procedures. This information will provide a large body of high quality data for clinical research on the factors influencing survival and quality of life following severe head injury. In addition, the data bank will serve as an efficient mechanism for collecting, storing and retrieving the information collected on a single patient and groups of patients. The number of therapies and monitoring devices commonly utilized during the acute phase of managing traumatic coma necessitates a highly organized data handling capacity.

Proposed Course of the Project: This was a three-year collaborative pilot project involving six centers which collected patient data, a Data Bank Maintenance Center, and OBFS staff which provided systems support, in collaboration with the Principal Investigators. During the first stage of its operation, effort was focused on refining the uniform vocabulary and developing data collection methods. The second stage was a test phase during which the vocabulary and procedures for collection, entry and retrieval were implemented on a trial basis. In the third stage, data were collected, entered, and subjected to a wide variety of data quality enhancement efforts. Currently, analyses of the data are being performed.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

Stanford Univ. (N01-NS-8-2390)

Title: Data Bank Maintenance Center for Pilot Data Bank Network Projects in Stroke and Traumatic Coma

Contractor's Project Director: Dr. James F. Fries

Current Annual Level FY'82: $96,000

Objectives: TOD-ARAMIS, renamed the "Data Bank Network", was the Data Bank Maintenance Contractor (DBMC) for the Pilot Projects to establish Data Bank Networks for Stroke and Traumatic Coma. During the three and one-half year contract period, the Data Bank Network system provided the host computer for these projects for data editing, storage, and retrieval, as part of the Time-Oriented Data Base (TOD) system. Data collected at pilot centers and entered into separately maintained Stroke and Coma data banks are available for retrieval within and among the pilot centers.

Major Findings: The Data Bank Network has created the computer schema for the Stroke and Coma Data Bank uniform vocabularies and developed methods for entering these data, as transmitted from the microprocessors located in each hospital, into the central data bank. The schema is a dictionary of data elements contained in the patient chart. Data entry personnel at the ten clinical centers have been trained and several retrieval programs have been developed and utilized for preliminary analyses and using standard statistical packages on the stored data.

Significance to the NINCDS Program and Biomedical Research: The Data Bank Maintenance Center is crucial to the success of the ten data banks which comprise the Pilot Data Bank Networks for Stroke and Traumatic Coma. It serves as the central data repository, maintains data integrity and provides programming and systems support to the ten centers. The availability of this database computer software has made these data bank networks feasible without extensive investment in new programming activity. Applying this system to stroke and traumatic coma is a first step in the development of an optimal system for a national data bank network for neurological disorders.

Proposed Course of Contract: The Maintenance Center is now focusing its activities on storage and retrieval for Stroke and Coma. The Coma data bank contractors have recently revised their vocabulary; the coma schema has been reconstructed to reflect the current vocabulary; and efforts are under way to transform existing data to the new format, where possible. Data are being entered at each center and are analyzed for errors by the automatic data check programs. This project has been completed and data is being transferred to DCRT.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

RESEARCH TRIANGLE INSTITUTE (NO1-NS-8-2383)

Title: Test of Study Design and Pilot Study for a National Survey of Epilepsy

Contractor's Project Director: Dr. Fred Bryan Jr.

Current Annual Level: $33,536

Objectives: This project was initiated to develop a new casefinding approach for ascertaining the frequency of cases of epilepsy. The previously used methods have serious deficiencies, and this proposal seeks to remedy them. The goal is to use pharmacies which fill prescriptions for anticonvulsive drugs, to lead to the physicians providing care and thus to the epileptics. In a national survey, estimates of the scope of the epilepsy problem could be obtained for the U.S. population by using techniques of probability sampling.

Major Findings: The design test has been completed by the Contractor. The pilot study will be completed this year.

Significance to the NINCDS Program and Biomedical Research: Morbidity surveys of relatively rare disorders are difficult to carry out for the U.S. population. One fundamental problem is that adequate numbers of cases for meaningful analyses may not be included in the sample of individuals selected for study due to stringent requirements for sampling a population. With epilepsy, the problem is compounded because of the perceived social stigma associated with having the disorder. The approach being tested in this contract will, if feasible, yield a cost-effective strategy for the sampling of epileptics who take anticonvulsive drugs. Furthermore, the privacy of the persons included in the study will be safeguarded to a great extent. If this strategy proves successful, a national survey of epileptics could be undertaken which would be invaluable to NINCDS and other organizations responsible for the planning of programs for epilepsy.

Proposed Course of the Project: The project is divided into two parts: a design test and a pilot study. The design test is on a small scale, and its chief purpose is to lead to the development of methodology for data collection from pharmacies and physicians and to aid in the design of the pilot study. The pilot study is on a larger scale, and its purpose is to resolve methodological issues which are raised by the investigators or were apparent after the design test. In addition, the pilot study will serve as a dry run for the procedures of the main survey. After the report on the pilot study has been studied carefully, a decision will be made on whether to embark on a national survey of epilepsy.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

WESTAT, INC. (NO1-NS-4-2336)

Title: Survey of Intracranial Neoplasms

Contractor's Project Director: Thomas G. McKenna

Current Annual Level: $ 0

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of intracranial neoplasms.

Major Findings: The main survey has been completed and the findings have been presented to NINCDS by the contractor in the form of a final report. The report has been reviewed and additional data have been collected from the hospitals and certain analyses have been redone to improve the quality of the findings. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in professional medical journals.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of intracranial neoplasms. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The main study has been completed and the final report was submitted by the contractor. After careful examination of the final report it became evident that certain ICDA categories needed to be examined in order to validate the findings before publication. Some of the participating hospitals furnished photocopies of selected patient records and the data has been reanalyzed. The clinical and epidemiologic findings have been prepared in an article which is ready to be submitted for publication in a neurological journal. This study has been completed.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

UNITED STATES BUREAU OF THE CENSUS (YO1-NS-7-0031)
UNIVERSITY OF MISSISSIPPI (NO1-NS-7-2357)

Title: Survey of Major Neurological Disorders in Copiah County Mississippi

Contractor's Project Director: Mr. Robert W. Mangold (Bureau of the Census); Dr. Armin F. Haerer (University of Mississippi)

Current Annual Level: $0 (Bureau of the Census); $0 (University of Mississippi)

Objectives: The primary objective of the proposal is to establish the prevalence of six major neurological and developmental disorders (cerebrovascular disease, convulsive disorders, cerebral palsy, psychomotor delay, Parkinson's disease, and dementia) in a well-defined population of southern blacks and whites. A secondary objective is to evaluate the sensitivity and specificity of certain screening questions by means of an item analysis at the close of the study. This analysis is needed because effective screening questions will be used in other morbidity surveys (e.g., the Health Interview Survey of NCHS).

Major Findings: Preparation of reports is continuing. Presentations are being scheduled for various professional meetings.

Significance to the NINCDS Program and Biomedical Research: At present, there are no adequate data on the prevalance of the six disorders of interest among southern blacks and whites in the United States. A number of studies suggest that stroke is more common among the black population. Mortality data and a few morbidity studies suggest that Parkinson's disease is less common among blacks. A biological explanation of this observation is that both melanin and dopamine are involved in the same metabolic pathway. Dopamine-deficiency in the basal ganglia has been found in patients with Parkinson's disease and is the rationale for the treatment of this condition with L-dopa. Blacks have a higher concentration of dopamine in the basal ganglia than whites which could explain a lower frequency of Parkinson's disease. On the other hand, it may be that blacks with this condition do not seek medical care or receive inadequate care. Mortality tabulations, with all of their biases, suggest that blacks have a predominance of epilepsy and cerebral palsy, but this requires confirmation with morbidity data. The magnitude of the dementia problem has not been studied in any United States population and Copiah County will provide some indication as to whether there is a racial and sex differential in the frequency of this group of conditions.

Proposed Course of the Project: The field operations for the main study were divided into two types of operations. The first was a household screening operation which was conducted by the Bureau of the Census. Residents of the study area were screened in their homes by means of a questionnaire administered by lay interviewers who were trained and supervised by the Bureau of the Census. The second type of operation was the examination of persons suspected of having one or more of the disorders of interest on the basis of responses given to questions from the screening questionnaire. The University of Mississippi provided senior, board-certified neurologists to accomplish the neurological examinations and to record the medical findings on forms designed especially for this study. After the close of field operations, the data were sent to the Bureau of the Census for processing. Staff of NINCDS, with the assistance of the Project Director from the University of Mississippi, are now analyzing the data and preparing scientific reports.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

WESTAT, INC. (NO1-NS-7-2379)
NATIONAL CENTER FOR HEALTH STATISTICS (2-YO1-NS-9-0043-05)

Title: National Hospital Survey of Disease
(formerly Comprehensive Disease Statistics Survey)

Contractor's Project Director: Westat, Inc. - Dr. Anita Schroeder
NCHS - Dr. Monroe Sirken

Current Annual Level: Contractor - $ 0
NCHS - 20,000

Objectives: The objectives are to test the feasibility of obtaining hospital incidence and prevalence data for cases identified from abstracted hospital records of a number of neurological and other disorders, from a redesigned Hospital Discharge Survey of the NCHS. A key objective of a successful study would be to develop a survey program that would permit the annual collection of data on these disorders in order to develop trends of their incidence and prevalence.

The national sample of short-stay hospitals would provide a stable base for special studies. These studies would include methodological problems such as multiplicity. It would also provide an unbiased sample of patients for periodic studies of special interest such as costs of illness, degree of disability, duration of illness, etc. Comparability of data collection methods, and protocols from the same sample of short-stay hospitals, would also permit comparison across disease lines.

Major Findings: The Feasibility Study has been conducted in a sample of 27 hospitals. The data have now been analyzed and individual disease reports are being prepared, as well as the final report covering the methodological issues. NCHS has been involved in this cooperative effort with NINCDS and has worked on many methodological and statistical problems of the survey.

Significance to the NINCDS Program and Biomedical Research: NINCDS has been conducting a program of surveys of neurological disorders. There is a need to consider a more comprehensive approach to the collection of disease statistics. First, there is a considerable degree of redundancy in the present approach, both within NINCDS, and, probably, across Institute boundaries. Redundancy leads to higher than necessary costs associated with the collection of disease statistics data. Second, the present approach leads to delays in obtaining current information, since there are a limited number of surveys which can be conducted at any one time. Third, the methods and protocols used by each contractor differ and this affects the comparability of data across disease lines. Fourth, and perhaps most important, these data provide planning information based on a limited time period, when in fact trend data, obtained on an annual, prospective basis, would better serve the program planning and program evaluation functions.

The development of a comprehensive system for the collection of disease statistics on a wide variety of diseases would be of great value to NINCDS and other NIH Institutes, for it would eliminate the four above-mentioned major problems.

This proposal would establish a cooperative and joint relationship between NCHS and NINCDS, and would provide for an NCHS collection of national health statistics of considerable interest to NINCDS, and potentially, to other NIH Institutes. It would, to the extent that incidence and prevalence data can be obtained from records at short-stay hospitals, supplant NINCDS data collection efforts. NINCDS would continue to analyze the data collected to meet its own program planning needs.

Proposed Course of the Project: In the Feasibility Study the contractor was responsible for the field work, data collection, and processing of the data. The disease algorithms were prepared by NINCDS staff with the aid of medical consultants and other participating NIH Institutes. The development of the sampling plan, counting rules, and selection of the participating hospitals was undertaken by the National Center for Health Statistics, under a separate interagency agreement.

After the final report of the Feasibility Study has been received and reviewed, a determination will be made as to what will be the next steps leading to the main National Study.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1982

NATIONAL INSTITUTE OF MENTAL HEALTH (1Y01-0-0004-00)

Title: ECA Dementia Supplement

Contractor's Project Director: William Eton, Ph.D.

Current Annual Level: $175,000

Objectives: The study will identify a group of demented individuals who are non-institutionalized and the type of dementia will be ascertained by means of a medical examination. An estimate of the social and economic costs will also be generated.

Major Findings: None. The data are still being collected.

Significance to the NINCDS Program: As the population of this nation ages, the dementias will become an increasing medical problem. There are currently no reliable data on the cost of these disorders and this information is needed to assist in future health planning efforts.

Proposed Course of the Project: This project is an add-on to an existing NIMH program of mental health surveys. After an initial screening for cognitive disability, the subjects who are disabled will be given a medical examination. A close relative or friend of those with verified dementias will be used to help establish the history of the disease and estimate the social and economic costs to the affected individual and their friends or relatives.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02238-06 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Project Network in Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Head, Computer Applications Section, OBFS OD, NINCDS

Other: Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
Barbara Nichols, Programmer, CAS, OBFS NINCDS
Sylvia Edelstein, Systems Analyst, CAS, OBFS, NINCDS
James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS
Irene Fishman, M.A., Statistician, CAS, OBFS, NINCDS
Dr. Albert Heyman, Duke University Medical Center
Dr. Jay Mohr, University of South Alabama College of Medicine
Dr. Thomas Price, University of Maryland School of Medicine
Dr. Philip Wolf, Boston University Medical Center, School of Medicine

COOPERATING UNITS (if any)
Duke University Medical Center, Durham, NC; Univ. of Maryland School of Medicine, Baltimore, MD; University of South Alabama, College of Medicine, Mobile, Ala.; Boston University Medical Center, Boston, MA

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives of the Pilot Stroke Data Bank were: a.) to develop a uniform method of data collection utilizing standard clinical nomenclature and data collection methods to obtain patient histories, diagnosis, treatment and outcome data in the course of routine care; b.) to implement an interactive data bank network enabling the pooling of clinical data among institutions for collaborative inter-institutional studies and to provide rapid access to large quantities of clinical data; and c.) to demonstrate the feasibiity of such a network, including the computer aspects, collaboration among a number of institutions, to serve as a model for neurological diseases and disorders. This project has met its immediate objectives. The collected data from this pilot on over 1100 stroke patients are being analyzed for studies of stroke course and diagnosis. The pilot project has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02408-04 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Clinical Databanks As a Resource for Epidemiologic Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Cynthia Gross, Ph.D., Biostatistician
Computer Applications Section, OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head, Computer Applications Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section, OBFS, OD, NINCDS

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Much has been written on the use of observational studies in epidemiological research. It will be necessary to apply many of the same epidemiologic techniques used in conventional observational studies to the clinical data bank. Work on determining which epidemiologic approaches are most appropriate for use with clinical data banks has begun in conjunction with the Pilot Stroke and Traumatic Coma Databank Networks (N01-NS-8-2309, 6, 7, 8; N01-NS-9-2302, 96, 97, 98). The current focus of this project has been quality assurance methods for use in multicentered clinical data banks.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02493-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Stroke Diagnosis: The NINCDS Data Bank Algorithm

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s: Selma Kunitz, Head, Computer Applications Section, OBFS, NINCDS
Jay P. Mohr, Neurologist, University of S. Alabama College of Medicine
Carlos Kase, Neurologist, University of S. Alabama College of Medicine
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS

Other: None

COOPERATING UNITS (if any)
Departments of Neurology: Boston University, University of South Alabama, University of Maryland and Duke University

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.15	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In conjunction with the NINCDS Pilot Stroke Data Bank Network (Z01 NS 02238-06 OBFS) a diagnostic classification schema for strokes was devised which consisted of cerebral pathology, vascular pathology, location, diagnostic source and diagnostic role. Approximately 1,100 stroke patients have been classified by this algorithm and the results are being analyzed for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02492-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Data Support for Diagnostic Algorithms of Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.P. Mohr, Head, Department of Neurology, University of South Alabama
C. Kase, Department of Neurology, University of South Alabama
J.M. Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

Others: I. Fishman, Statistician, Computer Applications Section, OBFS, OD, NINCDS
S. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Department of Neurology, Boston University, Department of Neurology and Neurosurgery, University of Maryland; Department of Neurology, Duke University; Dept. of Neurology, Univ. of South Alabama; Medical Center Stanford Univ.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Pilot Stroke Data Bank project has developed operational diagnostic algorithms for the classification of stroke type. This study utilizes data from the Stroke Data Bank to measure the operational uniformity and consistency of the application of the diagnostic algorithms to patients entered at the four participating stroke centers. Identification of factors common within a stroke type as well as factors that differ between stroke types provides a means for enhancement and verification of the algorithms.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02491-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Activities of Daily Living Following Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: P. Wolf, Department of Neurology, Boston University
J. Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

Others: I. Fishman, Statistician, Computer Applications Section, OBFS, OD, NINCDS
S. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Dept. of Neurology, Boston University; Dept. of Neurology and Neurosurgery, Univ. of Maryland; Dept. of Neurology, Univ. of South Alabama; Dept. of Neurology, Duke Univ.; Medical Center, Stanford Univ.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.20	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study attempts to establish the scores associated with activities of daily living as a measure of stroke outcome. This study is a component of the Pilot Stroke Data Bank Project. The influence of factors such as medical complications, age, site and type of lesion, on the stroke course and subsequent level of activities of daily living and performance and placement class of the patients will be examined at specific points in time. Each patient is expected to have a minimum of two years of follow-up.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02340-05 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Network Project in Coma

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS
Other: James M. Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
Irene Fishman, M.A., Statistician, CAS, OBFS, NINCDS
Sylvia Edelstein, Systems Analyst, CAS, OBFS, NINCDS
Barbara Nichols, Programmer, CAS, OD, NINCDS
Dr. Lawrence Marshall, University Hospital at San Diego, CA
Dr. Howard Eisenberg, University of Texas Medical Branch at Galveston, TX
Dr. John Jane, Univ. of Virginia, Charlottesville, VA
Dr. Donald Becker, Medical College of Virginia, Richmond, VA
Dr. Robert Grossman, Baylor University, Houston, Texas
Dr. Kamran Tabaddor, Albert Einstein Medical College, Bronx, NY

COOPERATING UNITS (if any) University Hospital at San Diego, CA; University of Texas Medical Branch at Galveston, Texas; University of Virginia Medical Center, Charlottesville, VA; Medical College of Virginia, Richmond, VA; Albert Einstein School of Medicine, Bronx, N.Y.; Baylor School of Medicine, Houston, TX

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Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A Pilot Traumatic Coma Data Bank Project has been implemented with the objectives of developing common data collection methods and a uniform clinical vocabulary to insure inter-center comparability for the collection of accurate data for multicenter studies of severe head injuries. This is a demonstration project intended to provide guidelines and protocols for expansion to additional centers and other neurological disorders. The data collection in the pilot has focused on refinement of measures of outcome following head trauma, comparing primary brain injury characteristics (accident details, injury types and location) with outcome, and exploring the impact of secondary insults to the brain (shock, hypoxia, elevated intracranial pressure) on outcome.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02516-01 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Traumatic Coma: Epidemiological Characteristics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI's: Cynthia Gross, PhD, Biostatistician, CAS,OBFS, NINCDS
Selma C. Kunitz, Head, CAS, OBFS, NINCDS
Other: Margaret Meadows, Statistical Assistant, CAS, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.20	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The pilot Traumatic Coma Data Bank has collected information on 681 patients with severe head injuries, drawn from six centers in the United States. These data are being analyzed to identify patterns of injury and type of accident as they vary from center to center, by patient demographic characteristics, season and time of day.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02498-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

CT Scan Observer Variability Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS

Other James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS NINCDS

Karlin Richardson, Programmer, CAS, OBFS, NINCDS

Dr. Thomas Gennarelli, Neurosurgeon, Univ. of Penn. School of Medicine

COOPERATING UNITS (if any)

University of Pennsylvania, School of Medicine

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A study of observer variability in CT Scan reading and coding was implemented utilizing identical sets of CT Scan polaroids and the CT Scan Data Collection form of the Pilot Traumatic Coma Data Bank. Readers were neurosurgeons participating in the Coma Data Bank (Z01 NS 02340-05 OBFS). The degree of agreement among readers was calculated by Kappa statistics and an item analysis was performed. Severity of errors was determined by a substantive analysis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02443-03 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Offline Data Entry System for Stroke and Coma Projects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Barbara Nichols, Programmer, CAS, OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head, Section on Computer Applications, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	.8	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A "front-end" general purpose software package was developed for the Data-point terminals in the Data Bank Centers, which allows data to be entered, edited and stored locally by time and date. The software operates with menu processing, in which a nonprogrammer can choose the options for data entry from a list. It produces screen images which replicate the order of data on the data collection record. During data entry, data are edited for valid numeric ranges, alpha-numeric checks, code lists, and special formats such as dates. A new communication discipline is being added to insure the accuracy of data transmission. Patient management reports were designed and are now being implemented to serve as tools for patient care at the Data Bank Network Centers.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02450-03 OBFS

PERIOD COVERED: October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Spinal Manipulative Therapy as Treatment for Musculo-Skeletal Dysfunction in Athletes. Formerly titled "Study of Efficacy of Spinal Manipulative Therapy on the Performance of Athletes"

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Peter Jokl, Assoc. Prof. of Orthopaedic Surgery, Director of Athletic Medicine, Yale University School of Medicine
Murray Goldstein, Acting Director, National Institute of Neurological and Communicative Disorders and Stroke, NIH
J.F. McAndrews, President, Palmer College of Chiropractic
William Weiss, Chief, Office of Biometry & Field Studies, NINCDS

Other: James M. Dambrosia, Mathematical Statistician, Office of Biometry and Field Studies, NINCDS

COOPERATING UNITS (if any)

Yale School of Public Health

LAB/BRANCH: Office of Biometry and Field Studies

SECTION: Office of the Chief

INSTITUTE AND LOCATION: NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.1	PROFESSIONAL: 0.1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project will evaluate the efficacy of spinal manipulative therapy for alleviating neuromuscular and musculo-skeletal problems that diminish athletic performance. A demonstration of the effectiveness of treatment will be provided by a randomized controlled clinical trial of student athletes at Yale University. The OBFS role in this project's responsibility is the design and analysis of the trial to be accomplished in close collaboration with the Yale University School of Medicine.

The study design is near completion. Completion of the proposal awaits a site visit to the proposed facilities at Yale; a meeting with officials of the Medical School; and meetings with exercise physiologists at Yale and the athletic trainers and other staff who will participate in the study.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02444-03 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Statistical coordinating center for the phenobarbital clinical study (previously titled "Cognitive and Behavioral Effects of Phenobarbital in Young Children").**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS

Others: Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS
Karin B. Nelson, Chief; Deborah G. Hirtz, Expert Consultant; Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Karlin Richardson, Programmer; Kenneth A. Elsner, Systems Analyst; Sylvia Edelstein, Systems Analyst; Section on Computer Applications, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS; University of Washington

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Statistical design considerations for the study were developed for the RFP, as well as the functions and organization of the statistical coordinating center.

During this fiscal year, precoded data forms, and computer systems for data entry and management are being developed in collaboration with the Computer Applications Section. The system will handle patient status and data tracking, data quality assurance, and production of simple charts and tables. Edited data will be transferred to the DCRT, NIH Computer for statistical analyses.

**[This study is to support the DNB/NDP/NINCDS contract study entitled: "Behavioral and cognitive side effects of phenobarbital used for prevention of febrile seizure recurrence." The project officer is Dr. Karin B. Nelson, DNB, NDP, NINCDS, and the contractor of the study is the University of Washington.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02484-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Statistical Coordinating Center for Communicative Disorders Program projects**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
P.I. Christy Ludlow, Communicative Disorders Program, NINCDS

COOPERATING UNITS (if any)
Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Statistical designs are being developed and sample sizes determined for three CDP, NINCDS, project plans. They are: a study of the acquisition of communicative skills through speech, sign or total communication in the congenitally deaf; a study to evaluate the outcome of language learning through speech and/or sign in the congenitally deaf; and a population-based cohort study to evaluate the impact and treatment of speech and language disorders in children. The status of this project is indeterminate due to lack of program funding.

**[This study is the OBFS/NINCDS portion of contract studies in communicative disorders. The project officer of the contracts would be Dr. Christy Ludlow, CDP, NINCDS. But these contract studies were not funded and thus inactive.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02502-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Medical Studies Database System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s: Karlin Richardson, Programmer, OBFS, NINCDS
Sylvia Edelstein, Systems Analyst, OBFS, NINCDS

Other: Ken Elsner, Systems Analyst, OBFS, NINCDS
Dr. Young Jack Lee, Mathematical Statistician, OBFS, NINCDS
Selma C. Kunitz, Chief, Computer Applications Section, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Computer Applications

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the Medical Studies Database System (MSDS) is to provide a computerized system that facilitates data handling functions with a high degree of automation that minimizes data collection errors and computer programming and provides forms-tracking, data updating with automatic audit-trail and user-friendly data retrieval. The methodology involves:

1) Entry of medical data from data collection forms onto Hewlett Packard 2647A Intelligent Terminal screens which mirror the data collection forms;
2) The transfer of the data to a data base management system (DBMS), Hewlett Packard's Image, on an HP-1000 minicomputer under RTE IVB operating system;
3) A forms-tracking system which records the validity status of the data;
4) Easy-to-use retrieval utilities.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02488-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Interactive Computer System for Patient Entry and Randomization for Clinical Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Young Jack Lee, Mathematical Statistician,
Section on Mathematical Statistics, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Laurie Burch, Programmer, Personal Service Contract

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An interactive computer system is under development. The system will utilize the TSO of the DCRT, NIH computer. The clinical trial operations office will register patients entering clinical trials, check the eligibility and perform random allocations of the treatment to eligible patients, all using the interactive system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02489-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Evaluation of the effectiveness of information services provided to specialists in communicative disorders by MEDLINE**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Christy Ludlow, Communicative Disorders Program, NINCDS
P.I. Barbara Reiner, Communicative Disorders Program, NINCDS
Others: Young Jack Lee, Section on Mathematical Statistics, OBFS, OD, NINCDS
Sylvia Edelstein, Systems Analyst, Section on Computer Applications, OBFS, OD, NINCDS
Karlin Richardson, Programmer, Section on Computer Applications, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.30	.20

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Five study centers are participating in evaluating the effectiveness of MEDLINE in information services provided to specialists in communicative disorders. User profiles and information needs are collected through preuse questionnaires. The Phase I data have been collected and entered into the computer. The Phase II data are being collected. The Phase II data form is under development.

** [This study is the OBFS/NINCDS portion of a larger contract study entitled: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE. The project officer is Dr. Christy Ludlow, CDP, NINCDS. Project numbers are N01-NS-0-2342, N01-NS-0-2343, N01-NS-0-2344, N01-NS-0-2345 and N01-NS-0-2346.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02310-06 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

A Statistical Study of Sensory-Decision-Theory Method in the Measurement of Experimental Pain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates statistically the nature of sensory-decision-theory (SDT) method in determining pain components from responses of experimental subjects to painful stimuli. The parametric approaches to the SDT method were evaluated for the estimability of, and the relationship between, sensory discriminability and response bias. Sampling behavior of these indices was also examined. A report has been prepared and the study has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02517-01 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Statistical Methodology for the Measurement of Pain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates the statistical problems involved in the Measurement of experimental and clinical pain. (1) A study has been conducted to investigate the statistical technique used in deriving psychophysical measurements of pain. A report has been prepared for the part of work dealing with sensory-decision-theory measures such as d' and β. Further study of the interrelationship among other types of measurement indices, e.g., p(A), Hodo's percent bias and MacNicol's index of response bias, B , are ongoing. (2) A study of statistical quantification of the temporal characteristics of persistent, episodic pain such as migraine headache is currently being developed. A group of measurements for this type of pain has been selected for further investigation. (3) A meeting is in preparation by the members of OBFS and other program areas of NINCDS to review the current state-of-the-art of the methodology for the measurement of pain. This meeting will justify the need for conducting a full-scale symposium to discuss various aspects of pain measurement problems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02504-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Epidemiological Study of Pain (Formerly titled Estimation of the Incidence Rate of Disabling and Severe Headache)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Thomas F. Drury, Ph.D., Office of Analysis and Epidemiology, NCHS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to evaluate the average and age-specific incidence rates of various chronic pain syndromes, and to investigate the relationship between occurrences of these pain conditions with various epidemiological factors. (1) The incidence rates of disabling and/or severe headache were evaluated with data obtained from a Mid-West non-clinical population survey. The relationship between incidence and prevalence rates and length of illness due to headache has been examined. A report of the results of this study has been prepared. (2) A study is currently being developed to evaluate the average and age-specific incidence rates of neck-back pain and low back pain based on the data from NCHS national surveys. The association of these pain syndromes with various demographic, psychological and medical-care variables will be investigated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02239-06 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Design of Health Interview Survey Questionnaire Supplements (Previously titled: "Design of Convulsive Disorder Questionnaires")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Frederic D. Weinfeld	Survey Statistician	OBFS NINCDS
OTHERS:	Dallas W. Anderson	Survey Statistician	OBFS NINCDS
	Herbert M. Baum	Demographer	OBFS NINCDS

COOPERATING UNITS (if any)

Clint Burnham, National Center for Health Statistics; W. Allen Hauser, Columbia University; Lee Kudrow, California Medical Clinic for Headache

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the design and field testing of questionnaires to be used as supplements to the NCHS's Health Interview Survey (HIS). The first such questionnaire was designed to collect information on the number of persons who had had a stroke, diagnosed or undiagnosed, and their hospitalizations. This questionnaire was included in the 1977 HIS. Questionnaires are being designed as supplemental modules for the HIS. One questionnaire will collect information on those persons with convulsive disorders. Another questionnaire will collect information on headache. The data collected will be used to provide national estimates of the prevalence of these disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02404-04 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

National Survey of Chronic and Debilitating Headache (Previously titled: "National Headache Survey")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Frederic D. Weinfeld	Survey Statistician	OBFS NINCDS
PI:	Ta-Chuan Chen	Mathematical Statistician	OBFS NINCDS
OTHER:	Dallas W. Anderson	Survey Statistician	OBFS NINCDS

COOPERATING UNITS (if any)
National Center for Health Statistics; California Medical Clinic for Headache; Cleveland Clinic; Diamond Headache Clinic; Headache Research Foundation

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.10	1.00	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to design a survey which would measure the prevalence, and describe the demographic characteristics of, major types of headache. The survey would also identify the clinical and environmental risk factors which may be associated with these headaches, and determine the impact of headaches on society. The survey questionnaire, which includes sections on demography, medical information and history, and cost, etc., has been developed. In the Feasibility Study (Phase 1), patients from four well-respected headache clinics have been solicited for a telephone interview about their headache problems. Information in the physician files about the headaches has been abstracted, coded, and computerized. This will be used as a basis for the investigation of validity of the telephone data. Plans for an Area Survey (Phase 2) have also been made.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02495-02 OBFS

PERIOD COVERED: October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analysis of Data From the National Survey of Multiple Sclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Herbert M. Baum	Demographer	OBFS NINCDS
OTHERS:	Karlin Richardson	Programmer	OBFS NINCDS

COOPERATING UNITS (if any)

Beth Rothschild, National Analysts; Labe Sheinberg, Nicholas LaRocca, and Alice Kornblith, Albert Einstein College of Medicine

LAB/BRANCH: Office of Biometry and Field Studies

SECTION: Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION: NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.70	.60	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The National Survey of Multiple Sclerosis (NSMS) is a probability sample of all multiple sclerosis patients in the conterminous United States. The Survey gathered detailed data on the disease, employment, and social history of over 1200 cases. The Office of Biometry and Field Studies, in conjunction with other researchers in the field of multiple sclerosis, is undertaking a detailed analysis of these data. It is hoped that we will obtain an understanding of how disease factors affect the lives of individuals with multiple sclerosis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02499-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Stroke Incidence in South Alabama

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s: Cynthia Gross, Ph.D., Biostatistician, OBFS, NINCDS
Dr. Jay Mohr, neurologist, University of S. Alabama College of Medicine
Dr. Carlos Kase, neurologist, University of S. Alabama College of Medicine.

Other: None

COOPERATING UNITS (if any)

University of South Alabama, College of Medicine, Mobile, Alabama

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.25	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As a component of the Pilot Stroke Data Bank (N01 NS 8-2397), 1980 stroke incidence data has been collected for the population of a well-defined geographic area located in three counties in southern Alabama. About 160 persons hospitalized with a stroke which occurred in 1980 were identified from a population of about 100,000 persons. These data provide incidence rates by age, sex, race, and stroke type. The age adjusted incidence rate for blacks was almost twice the rate for whites. Medical history as well as other factors were collected for each stroke case. Two-thirds of the stroke cases had a history of hypertension and one in five had a history of diabetes. These data are presently being analyzed for a publication which will compare these findings with other similar studies of stroke.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02406-04 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Frequency of Neurological Disorders Among Hospital Discharges

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum Demographer OBFS NINCDS

COOPERATING UNITS (if any)

Donald Smith, National Center for Health Statistics

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Hospital Care Statistics Branch, of the National Center for Health Statistics, has agreed to provide us with data on neurologically related hospital discharges. A list of conditions, using ICDA-8 codes, of primary interest to the Institute was prepared. By examining data on the first-listed and on all listed diagnoses at the time of discharge we can monitor secular trends. This will become an annual reporting effort. This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02405-04 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Assessment of Strategies for Analyzing Data from Small Area Health Surveys (Previously titled: "Assessment of Strategies for Analyzing Data from Small Area Mortality Surveys")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas W. Anderson Survey Statistician OBFS NINCDS

COOPERATING UNITS (if any)

W. Edwards Deming, Washington, D.C.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.09	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies of small areas, such as communities or counties, are an important tool of epidemiologists, who are interested in studying distributions of diseases in populations. Many studies of this type have been reported in the scientific literature. An assessment of techniques of analysis frequently used in these studies was initiated to determine their adequacy for use in the NINCDS survey of major neurological disorders in Copiah County, Mississippi (YO1-NS-70031, NO1-NS-7-2357).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02515-01 OBFS

PERIOD COVERED: October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Study of Hearing Disorders Among the Aged

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Eve K. Moscicki	Scientist	OBFS NINCDS
OTHERS:	Herbert M. Baum	Demographer	OBFS NINCDS
	Earleen Elkins	Audiologist	CDP NINCDS

COOPERATING UNITS (if any)

Patricia McNamara, FES, NHLBI

LAB/BRANCH: Office of Biometry and Field Studies

SECTION: Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION: NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.25	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Hearing data collected during Cycle 15 of the Framingham Heart Study (1978-1979) will be analyzed to estimate the prevalence of hearing impairment among the Framingham cohort. The risk factors that might be associated with hearing loss found in this population will also be examined.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02494-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Prevalence of Multiple Sclerosis in Colorado

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum Demographer OBFS NINCDS

COOPERATING UNITS (if any)
D. Thompson, L. Nelson, and J. Burks, Rocky Mountain Multiple Sclerosis Center

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.20	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Rocky Mountain Multiple Sclerosis Center is one of a few centers devoted solely to the care of patients with multiple sclerosis, and is the only center of its type in the State of Colorado. Using records from the Center, local multiple sclerosis societies, and the local chapter of the National Multiple Sclerosis Society we will attempt to estimate the incidence and prevalence of the disease for Weld and Larimer Counties. If this effort is successful, we might try to get an estimate for the State. Other collaborative efforts are also anticipated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02312-06 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Maternal Infection Study**
(previously titled "Methodology for Systematic Analysis of Multiple Antibody Readings on Matched Controlled Studies")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS
John L. Sever, Chief, Infectious Diseases Branch, IRP, NINCDS
Other: Alan Talbert, Mathematical Statistician, OBFS, OD, NINCDS
Martha Griswold, Statistician, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, IRP, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analysis of the Collaborative Perinatal Project (CPP) data continues in the area of maternal infection. (The CPP is a prospective study of approximately 60,000 gravidae and the follow-up of their children through the seventh year of life.) The relationship of maternal infection during pregnancy with the later status of the child is being examined using both clinical and serologically-confirmed infections in the mother.

**(This study is the OBFS/NINCDS portion of a larger study entitled: Perinatal Infections Causing Damage to the Child - Collaborative Perinatal Project, Z01 NS 00402-26 ID. The principal investigator on the overall study is Dr. John L. Sever, Chief, IDB, IRP, NINCDS.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02114-09 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Etiology and Natural History of Convulsive Disorders and Cerebral Palsy**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS
P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	.9	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study examines the relationship between perinatal and early postnatal factors and the occurrence of seizure disorders and cerebral palsy in childhood. The project derives from the data of the Collaborative Perinatal Project, a large prospectively-followed population (approximately 60,000 mothers, with their children followed to seven years of age). The univariate screen of maternal, obstetric and pediatric risk factors, and demographic analysis have been completed. Multivariate assessment of the data bank is in progress including correlation and regression analysis. Selected topics of particular clinical relevance are under examination.

** [This study is the OBFS/NINCDS portion of a larger study entitled: Convulsive Disorders Data Analysis Group, Z01 NS 02058-10 DNB and Cerebral Palsy Data Analysis Group, Z01 NS 02059-10 DNB. The principal investigator for these studies is Dr. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02483-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Predictive Value of the EEG in Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS
Nikola Sofijanov, Pediatric Neurologist, University of Skopje, Yugoslavia
Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Deborah G. Hirtz, Pediatric Neurologist, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

Other: Frances Canning, Forms Design, DNB, NDP, NINCDS
Sylvia Edelstein, Senior Programmer, Computer Applications Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Pediatric Clinic, University of Skopje, Yugoslavia

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Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.10	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study will evaluate the significance of the EEG as a predictor for recurrence of seizures in those children who have had a simple febrile convulsion. Outcome with respect to febrile seizure recurrence and afebrile seizure occurrence will be reported. The evolution of the EEG pattern will be described, and patterns will be correlated with the clinical outcome. The clinical study is being carried out in Skopje, Yugoslavia, at the Pediatric Clinic of the University of Skopje.

The study began in FY'82 and will be completed in FY'87. Completed during FY'82 were the data management and quality control systems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02411-04 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Survey of Practice in the Management of Febrile Seizures (previously titled "Survey of Management of Children with Febrile Seizures").

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
P.I. Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS
P.I. Deborah G. Hirtz, Pediatric Neurologist, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.15	.15

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A survey of clinical practice in the management of febrile seizures is ongoing. The survey form has been submitted for OMB clearance. The survey of approximately 10,000 physicians in various specialities will determine which medical discipline(s) treats most children with febrile seizures, what criteria physicians use to determine therapy, the regimens prescribed and the specific goals of therapy.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02497-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

INDO-U.S. Study of Head Injury

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s: William Weiss, Chief, OBFS, NINCDS
Dr. John Jane, Chairman, Dept. of Neurological Surgery, Univ. of VA, Charlottesville, VA
Dr. Prakash Tandon, Chairman, Dept. of Neurosurgery, All-India Institute for Medical Research, New Delhi, India

Other: Rebecca Rimel, R.N.N.P., Univ. of VA, Charlottesville, VA
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS

COOPERATING UNITS (if any)
University of VA. Dept. of Neurosurgery, Charlottesville, VA
All-India Institute of Medical Science, New Delhi, India

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.10	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Information on head-injured persons has been collected in independent research efforts in Charlottesville, Virginia, and in New Delhi, India. A preliminary review of these data collection efforts has indicated significant overlap in the type of information collected. A preliminary analysis of the collected data is proposed to identify differences and similarities between these head-injured populations, and to determine the feasibility of a prospective cooperative association for the study of head injuries.

The Government of India has approved the research proposal and has allocated 767,000 rupees for the three-year Indian portion of the collaborative study. The proposal will now enter the NIH review process.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02518-01 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Neurological Aspects of Aging in Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Manuel Martinez-Maldonado, Chief, Medical Service & Director
Renal Metabolic Laboratory, Veterans Administration Center,
San Juan, Puerto Rico
Efran Toro Goyco, Chairman, Dept. of Biochemistry
University of Puerto Rico Medical School, San Juan, Puerto Rico
Donald Price, Professor, Dept. of Neurology
University of Maryland School of Medicine

Other: William Weiss, Chief, OBFS, NINCDS
James Dambrosia, Ph.D., Acting Chief,
Section on Math. Stat., OBFS, NINCDS

COOPERATING UNITS (if any)
Medical School, University of Puerto Rico, San Juan, Puerto Rico
Veteran Administration Center, San Juan, Puerto Rico
Johns Hopkins University

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project will be a consortium of center grants and individual investigator grants to study the neurologic aspects of aging in Macaca mulattas. The University of Puerto Rico will provide the facilities of the Caribbean Primate Research Center and investigators in behavioral research at Cayo Santiago and Sabana Seca. Investigators with individual research projects from the University of Puerto Rico and the Veterans Administration Hospital in San Juan will use the primate facilities. Dr. Price and his colleagues at Johns Hopkins University will map neurotransmitter pathways in the young, adult, and aging primate brain. OBFS will provide the computer facility and a statistical coordinating center to process the data and to collaborate on identifying associations across individual project boundaries.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02481-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
The Use of Phantom Views to Diminish an Artifact in CT Scans

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. George H. Weiss, Chief, Laboratory of Physical Sciences, DCRT
P.I. Alan J. Talbert, Statistician, OBFS, OD, NINCDS
P.I. Rodney Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS

COOPERATING UNITS (if any)
Laboratory of Physical Sciences, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An artifact in computed tomography scans which occurs with too few views is the appearance of streaks at some distance from the image causing them. The phantom views method consists of inserting phantom data points, obtained by interpolation between real data points. This study shows that the phantom views method does diminish this artifact and finds the optimum number of phantom views. This study has been completed and a paper has been accepted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02482-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Optimization of Software for PET Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Alan J. Talbert, Statistician, OBFS, OD, NINCDS
P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS

COOPERATING UNITS (if any)
Neuroradiology and Computed Tomography Section
Surgical Neurology Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.6	.6	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Software is being developed for a PET scanner which is being constructed by the Neuroradiology and Computed Tomography Section. The picture processing program is being optimized for speed and accuracy. This involves the use of low level languages and intimate knowledge of image processing mathematics and the computer architecture. Substantial improvements in execution time have been achieved. Further improvements are being developed.

** [This study is the OBFS/NINCDS portion of a larger study entitled: Development of a High Resolution Positron Emission Tomograph. The Principal Investigator is Dr. Rodney Brooks, Neuroradiology and CT Section, SNB, IR, NINCDS.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02486-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Statistical models of in vitro mutagenicity assays

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
P.I. William J. Caspary, National Toxicology Program, National Cancer Institute

COOPERATING UNITS (if any)
National Toxicology Program, National Cancer Institute

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Chemically-induced genetic damages of cells (mammalian or submammalian) in vitro are observable by allowing the cells to express their DNA damage and the progenies with locus-specific mutation to be selected and form colonies.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02519-01 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Case-Control Studies of Antiviral Antibodies in Multiple Sclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Joanna Woyciechowska, Infectious Diseases Branch, IRP, NINCDS
John L. Sever, Infectious Diseases Branch, IRP, NINCDS
Other: James M. Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Levels of antiviral antibodies from MS patients are compared to those of matched control subjects in an attempt to establish possible alteration of immune responses in patients with MS. One component of the study uses 24 twin pairs, and another has 99 MS patients with controls matched on age, sex, geographic location, and migration history. This project has been completed.

** [This study is the OBFS/NINCDS portion of two larger studies entitled: Non-viral Antigens in Perinatal and Neurological Disease, Z01 NS 01985-11 ID, and Combined Clinical, Viral and Immunological Investigation of Acute and Chronic Diseases of the Central Nervous System, Z01 NS 02038-10 ID. The principal investigator of the former project is Dr. David Madden, IDB/IRP/NINCDS and that of the latter is Dr. John Sever, IDB/IRP/NINCDS.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02446-03 OBFS

PERIOD COVERED
October 1, 1981, through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Parkinson's Disease in Twins
(previously titled "Parkinson Twin Studies")**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. R. Eldridge, Section on Neuroepidemiology, IRP, NINCDS
P.I. C. Ward, Experimental Therapeutics Branch, IRP, NINCDS
P.I. J. Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Experimental Therapeutics Branch, IRP
Section on Neuroepidemiology, IRP

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Twin pairs, discordant with respect to Parkinson's disease, are evaluated for zygosity and the presence of Parkinson disease. Clinical, laboratory, historical, and psychometric data are obtained for both the pro-band and the co-twin. Statistical analysis of these matched pairs will attempt to identify risk factors and examine differences between the pro-bands and co-twins.

** [This study is the OBFS/NINCDS portion of a larger study entitled: "Genetic Epidemiology Studies in MS and Other Multifactorial Neurologic Disorders" (Z01 NS 02167-06 ODIR). The principal investigator on the overall study is Dr. Roswell Eldridge, NES, ODIR.]

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02490-02 OBFS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Research in Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James M. Dambrosia, Acting Chief, Section on Mathematical Statistics, OBFS, OD, NINCDS
Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
Alan Talbert, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
Jonas H. Ellenberg, Acting Deputy Chief, OBFS, OD, NINCDS

OTHER: None

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.65	.65	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project addresses statistical problems generated from collaboration with scientists in other program areas and general statistical problems of current interest. This project is a continuing activity of the Section on Mathematical Statistics.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02514-01 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Review of Techniques for Sampling of Rare Populations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas W. Anderson Survey Statistician OBFS NINCDS

COOPERATING UNITS (if any)

W. Edwards Deming, Washington, D.C.; Monroe Sirken, National Center for Health Statistics

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.01	.01	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Special techniques of sampling are required for surveys of rare characteristics in populations, as ordinary approaches would be impractical. This investigation provides a compilation and assessment of sampling techniques used successfully in population studies of rare characteristics. This assessment is made in light of the Institute's need for surveys of relatively rare neurological disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02506-02 OBFS

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Antibody Titers in Macacas on Cayo Santiago

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: William T. London, Chief, Experimental Pathology Section, IDB, IR, NINCDS

Other: William Weiss, Chief, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, IR, NINCDS

LAB/BRANCH Office of Biometry and Field Studies

SECTION Office of the Chief

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland, 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project will provide a test of four antigens on adult and juvenile Macacas on Cayo Santiago, Puerto Rico. One problem is to determine the percent of positive antibody titers that can be determined from the adult sample for whom blood sera are presently available, and the number of juveniles that should be sampled.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02415-04 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cage Standards for Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Dr. William T. London, Chief, Experimental Pathology Section, IRP, NINCDS

Other: James Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	0.10	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Present cage assignments for primates are based solely on the animals' weight. Variation in shape between species of primates of the same weight indicate that the current weight-based standard may be inappropriate. A large number (410) of primates of four different species have been measured (arms, legs, chest, tail, crown to rump, crown to heel) in order to determine association of and variations in weight as functions of shape measurements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02496-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Preliminary Steps for a Data Bank Project in Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s: Selma C. Kunitz, Chief, CAS, OBFS, NINCDS
Cynthia Gross, Ph.D., Statistician, CAS, OBFS, NINCDS
William Weiss, Chief, OBFS, NINCDS

Other: Nikola Sofijanov, Visiting Scientist, OBFS, NINCDS
W. Allen Hauser, M.D. Neurologist, Sergievsky Institute, N.Y., N.Y.

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For a data bank to be effective in clinical research, there must be a clear delineation of the research questions that will be addressed. An initial step, then, in proposing a data bank is developing a list of appropriate research questions and hypotheses. A broad set of research questions for a potential data bank in epilepsy has been suggested.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02501-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Myasthenia Gravis Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Irene G. Fishman, Statistician, CAS, OBFS, OD, NINCDS
Selma C. Kunitz, Chief, CAS, OBFS, OD, NINCDS

Other: Ken Elsner, Systems Analyst, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Christopher Clark, M.D., Elliott Neurological Center of the Pennsylvania Hospital, Philadelphia, PA.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project involves consultation to a group of neurologists who are interested in the possibility of collecting clinical information on patients with myasthenia gravis. An initial set of parameters to be collected has been proposed, the first version of forms has been redesigned, and data is being collected on demographics, initial evaluation, and subsequent follow-ups. This project is currently in progress. OBFS staff is acting only in a consultative role to this extramural group of investigators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02341-05 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Type-Specific Stroke Mortality Trends

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Herbert M. Baum	Demographer	OBFS NINCDS
OTHERS:	Murray Goldstein	Acting Director	NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The investigators used the NCHS mortality data tapes for 1968-1976 to examine age-type-specific stroke mortality trends by race, sex, and hypertension status. There are many problems inherent in arriving at conclusions in a study based on death certificates, but the study explores the shortcomings of the data to arrive at implications. A general decline in stroke death rates was observed with the largest declines being observed for hemorrhagic strokes and for nonwhites. An examination of the data by hypertension status indicates the need for clinical studies which will examine the relationship between hypertension and stroke mortality. This project is now completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02442-03 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Feasibility of a National Survey of Speech Defects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Herbert M. Baum	Demographer	OBFS NINCDS
OTHERS:	Eve Moscicki	Scientist	OBFS NINCDS
	Christy Ludlow	Speech Pathologist	CDP NINCDS

COOPERATING UNITS (if any)

Communicative Disorders Program, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

National data on the incidence and prevalence of communicative disorders are scarce. An investigation of the feasibility for gathering such data has been undertaken. One plan is to conduct a survey of both providers and cases. This approach will permit us to also gather data on the cost of the problem, type of services needed, amount of services needed, etc. This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02447-03 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
A Prospective Study of Low Birthweight Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Acting Chief, Mathematical Statistics Section, OBFS, OD, NINCDS

P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)
Children's Hospital of Washington, D.C.
Section on Cerebral Palsy and Other Motor Disorders, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All low birthweight (1750gm or less) infants referred to Children's Hospital are examined, CAT scanned for hemorrhage, and evaluated by the Hospital staff. Specified information is collected prospectively on each child until the age of three years. The objective of the study is to identify risk factors associated with neurological deficits, in particular CP. This project has been terminated due to the unavailability of staff and funds at Children's Hospital.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02503-02 OBFS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cerebral Palsy Bibliography of Selected References

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Naomi M. Hawkins, Technical Information Specialist, OBFS, OD, NINCDS

Other: Karin B. Nelson, M.D., Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

Jonas H. Ellenberg, Ph.D., Acting Deputy Chief, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS and Section on Mathematical Statistics, OBFS, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Preparing a bibliography on cerebral palsy with selected references covering etiology, risk, diagnosis, prognosis, prevalence and incidence and history. This project has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02414-04 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Early Stopping Rules Used in Clinical Trials previously titled "Simulation of Early Stopping Rules Used in Clinical Trials".

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

P.I.: Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project assesses the various techniques proposed for early stopping of clinical trials in the face of unexpected evidence of the failure or success of a particular regimen, prior to the scheduled termination of a trial.

Distribution theory for these procedures is either mathematically intractable or only known asymptotically. A computer simulation study for comparison of the various procedures is being considered.

OBFS organized an invited paper session at the Spring 1981 Biometrics meeting concerning this topic. The papers from this session have been published and this project is completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02500-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Polymyositis/Dermatomyositis Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Irene G. Fishman, Statistician, CAS, OBFS, OD, NINCDS
Selma C. Kunitz, Chief, CAS, OBFS, OD, NINCDS

Other: Ken Elsner, Systems Analyst, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Christopher Clark, M.D., Elliott Neurological Center of the Pennsylvania Hospital, Philadelphia, PA

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The low incidence of myositis and its chronic course necessitate collaboration of a number of investigators. The project involves consultation by OBFS staff to a group of neurologists who are considering the possibility of collecting clinical information on myositis patients. An initial set of data items for collection has been proposed, and forms were designed to enter data on demographic information, initial evaluation, and subsequent follow-up. These forms were distributed to interested researchers, and refinements were made incorporating experience with their use. The revised set of forms will be discussed at their next meeting in the Fall of 1982. OBFS staff is acting only in a consultative role to this extramural group of investigators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02480-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

A Clinical Study of Bromocriptine and Pergolide for the Treatment of Parkinson's Disease**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: J.M. Dambrosia, Acting Chief, Mathematical Statistics, Section, OBFS, OD, NINCDS

P.I.: P. LeWitt, Experimental Therapeutics Branch, IRP, NINCDS

P.I.: D. Calne, Head, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS (if any)

Experimental Therapeutics Branch, IRP, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project assesses the relative efficacy of Bromocriptine versus Pergolide for the treatment of Parkinson's disease. A randomized, double-blind, two-period crossover trial with washout periods is employed to evaluate treatment of forty outpatients. Patient responses are measured objectively by computer sensing equipment and clinically using a modified Columbia rating scale. Adverse reactions are monitored throughout the trial. This project is completed.

**(This study is the OBFS/NINCDS portion of a larger study entitled: Therapeutic Studies in Parkinsonism and Other Movement Disorders, Z01 NS 02258-05 ET. The Principal Investigator on the overall study is Dr. Thomas Chase, Acting Chief, Experimental Therapeutics Branch.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02505-02 OBFS

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Headache in Pregnant Women

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

Other: Karin Nelson, M.D., Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Sylvia Edelstein, Systems Analyst, OBFS, NINCDS

COOPERATING UNITS (if any)

Paul Nichols, Ph.D., Developmental Neurology Branch, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.2	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates the relationship between migraine headache and pregnancy based on the data collected from a large group of women in pregnancy the Collaborative Perinatal Project gravidae. Subgroups of pregnant women characterized by the absence and presence of migraine and other recurrent headaches prior to or during pregnancy, are identified. Characteristics of these subgroups are investigated on a variety of demographic, sociological, medical and obstetric factors, and the association of headache with other disorders. Seven data files were created bearing information of migraine history, use of headache medications, and frequencies of headache during pregnancy. Preliminary results showed pregnant women with a migraine history had more other symptoms and illnesses during their pregnancies than women without a migraine history. Children of mothers with a history of migraines appear to have higher incidence of seizures than children born to mothers in the non-migraine group. More careful statistical analyses will be carried out.

TAB 2 -- EXTRAMURAL ACTIVITIES PROGRAM -- EAP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Extramural Activities Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981, through September 30, 1982
Director's Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Extramural Activities Program (EAP), NINCDS, was organized in July, 1975, to serve as the Institute center for science administration and fiscal management of the grant, fellowship, and research contract programs. The structure of EAP includes components responsible for manpower, scientific merit review, contract management, grants management, committee management, data reporting and analysis, and program support services including processing.

The senior staff of EAP consists of:

Director
Deputy Director
Chief, Scientific Review Branch
Chief, Contracts Management Branch
Chief, Grants Management Branch
Chief, Office of Data Analysis and Reports

Staff carries out an overall coordinating and supervisory function in regard to the implementation of recommendations of the NANCDS Council and Contract Advisory Committees, and the processing and issuance of proposals and awards in the respective program areas. The Director, EAP, in consultatation with the Director of NINCDS, works closely with the other Program Directors on questions of policy relating to the NINCDS extramural programs.

More specifically, the Extramural Activities Program coordinates grant and contract programs for the NANCDS Council, the Program Directors, the Contract Review Board, the Training Board, the Program Staff, and the Extramural Staff. The EAP studies and supervises certain program processes, e.g., distribution of awards during the four quarters of the fiscal year; prepares summary data, e.g., the Research Grant and Fellowship Data Books; and provides fiscal information, e.g., Fiscal Status Reports, Percentage Funding Rates, and develops alternate strategies for various budget levels.

One major personnel change is as follows: Dr. Marilyn Semmes, formerly Director of Special Projects, Head Start Bureau, joined the staff of the Scientific Review Branch as Executive Secretary, Communicative Disorders Review Committee. Dr. Semmes replaces Dr. Ernest J. Moore, who joined the staff of the Communicative Disorders Program, NINCDS, earlier in the year.

In summary, the Extramural Activities Program provides for the Director of the Institute and the Directors of the Program Areas scientific, fiscal, and administrative management support services.

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Research Grants Program
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Research Grants portion of the NINCDS Annual Report provides an overall summary of administrative developments as they pertain to research grants. Other activities such as training awards, contracts, etc., are mentioned here merely to provide an overview, and are discussed in more detail elsewhere.

The research grant, contract, and training programs of the NINCDS are focused on the identification, stimulation, and support of essential research problems aimed at the improved diagnosis, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, and human communication. They include disorders affecting the development and maturation of the nervous system (developmental disorders, motor and convulsive disorders, and demyelinating and degenerative disorders); disorders caused by extrinsic insults (central nervous system infections, stroke, trauma, neoplasms); and disorders in human communication (hearing, speech, language, the vestibular system, other senses, and behavior). Research support is also provided in the area of fundamental neuroscience which is appropriate to the Institute's mission, but not related to any specific disorder. Included are nerve structure and function studies and investigations of the development of various types of prostheses. The administrative instruments used to accomplish these purposes include research projects, research program projects, clinical research centers, research career awards, research career development awards, teacher-investigator awards, institutional research fellowship awards, individual research fellowship awards, and contracts.

The following Table shows the number of research grant applications considered by the Council at its spring meetings over the past five years.

MAY '78	MAY '79	MAY '80	MAY '81	MAY '82
600	645	618	685	644

Over the past five years, there has been a significant increase in the number of applications reviewed. This may be attributed partially to the effectiveness of the research training programs of the Institute from which the output of fully trained investigators has reached its full potential only in recent years.

The following Table shows the number of research grants (R's and P's) awarded and the total amounts of funds expended (in millions) each year for the past five years.

	FY '78	FY '79	FY '80	FY '81	FY '82
NUMBER	1,149	1,391	1,553	1,505	1,559
DOLLARS	$106.4	$132.2	$160.7	$171.0	$181.0

Table I (on the following page) shows the number of awards and the amounts of funds expended for each type of award within each Program Area.

TABLE I

Number of Awards and Dollars* Expended by Program Area and Type of Award

PROGRAM AREAS

TYPE OF AWARD	CD		FN		ND		ST		TOTAL	
	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars
Research Grants	260	$ 22.2	410	$ 32.3	598	$ 51.1	177	$ 16.7	1445	$ 122.3
Program Projects and Clinical Centers	25	13.2	10	3.6	37	19.6	42	22.3	114	58.7
Contracts	12	1.3	17	2.6	17	3.0	9	1.6	55	8.5
Training Grants	11	.8	26	1.8	24	1.8	6	.3	67	4.7
Fellowships	38	.7	91	1.6	38	.7	24	.4	191	3.4
Teacher Investigator Awards	20	.8	0	0	66	2.9	24	1.0	110	4.7
Research Career Development Awards	16	.6	25	1.0	23	.8	10	.4	74	2.8
Research Career Awards	1	**	0	0	3	.1	1	**	5	.1
GRAND TOTAL	383	39.6	579	42.9	806	80.0	293	42.7	2061	205.2

*Dollars in millions
**Less than $50,000

October 1, 1981-September 30, 1982

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Manpower Programs' Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Institute has four training programs. Two programs, the Individual National Research Service Award (NRSA) and the Institutional National Research Service Award, are funded from the $8.078 million available in the FY '82 budget for training. The other two programs, the Research Career Development Award and the Teacher Investigator Development Award, are funded from FY '82 funds available in the "Other Research" category.

National Research Service Awards for Institutional Grants (Training Grants)

From FY '82 funds, the Institute provided continuation support for 42 Institutional NRSA's and made 25 new and renewal awards to support the following number of programs, according to NINCDS Program Area:

Program Area	New and Renewal Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	4	$ 380	7	$ 419	11	$ 799
Fundamental Neurosciences	9	719	17	1,111	26	1,830
Neurological Disorders	10	657	14	1,104	24	1,761
Stroke and Trauma	2	134	4	204	6	338
Total	25	$1,890	42	$2,838	67	$4,728

*Amounts in thousands

In the training grant program, funds are being provided for 44 predoctoral trainees and 216 postdoctoral trainees. In addition, about 148 short-term trainees were supported in summer programs.

National Research Service Awards for Individual Postdoctoral Fellows (Fellowships)

From FY '82 funds, the Institute provided continuation support for 89 fellows and made 102 new and renewal awards. A number of supplemental awards were also made but this did not increase the number of individuals being trained. The National Research Service Award for Senior Fellows is now in its third year of operation. The Institute made three awards totalling $81,000 during this FY '82. It is expected that a larger number of awards will be made in future years as this program becomes more visible. In total, awards were made to support the following number of fellows, according to NINCDS Program Area:

Program Area	New and Renewal Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	19	$ 325	19	$ 341	38	$ 666
Fundamental Neurosciences	51	889	40	688	91	1,577
Neurological Disorders	20	368	18	322	38	690
Stroke and Trauma	12	195	12	222	24	417
Total	102	$1,777	89	$1,573	191	$3,350

*Amounts in thousands

Research Career Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation RCDAs, according to the NINCDS Program area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	1	$ 37	15	$ 555	16	$ 592
Fundamental Neurosciences	7	278	18	708	25	986
Neurological Disorders	2	72	21	793	23	865
Stroke and Trauma	1	38	9	351	10	389
Total	11	$ 425	63	$2,407	74	$2,832

*Amounts in thousands

Teacher Investigator Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation TIDAs, according to NINCDS Program Area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	3	$ 125	17	$ 707	20	$ 832
Fundamental Neurosciences	0	0	0	0	0	0
Neurological Disorders	16	705	50	2,093	66	2,798
Stroke and Trauma	4	169	20	858	24	1,027
Total	23	$ 999	87	$3,658	110	$4,657

*Amounts in thousands

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Grants Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Grants Management Branch (GMB) consists of two sections, the Grants Administration Section and the Grants Processing Section. There are 22 people in the branch, with 11 people in each section. The Grants Administration Section is responsible for the administrative management of the research and training programs which are funded through a variety of assistance mechanisms, i.e., research project grants, program project grants, specialized center grants, training grants, fellowships, and career development awards. In addition, the Grants Administration Section has the responsibility for coordinating NINCDS responses to Freedom of Information requests. The Grants Processing Section is responsible for processing the grant applications for research, training, fellowship, and career development grant programs, for ensuring that funds are appropriately encumbered, and for preparing the books for the Advisory Council meetings.

During Fiscal Year 1982 the GMB will be responsible for a total grant budget in excess of $198 million, of which approximately $189 million will be for research grants and $9 million will be for training grants. The total represents a 4.8% increase over that for Fiscal Year 1981. Although there has been an increase in the FY'82 total grant budget, the number of awards issued probably will not similarly increase. This is because the cost of conducting research has been increasing at a rate in excess of that of the NINCDS grant budget. Nonetheless, approximately 2,217 applications will be reviewed at the three NANCDS Council meetings held during Fiscal Year 1982.

During Fiscal Year 1982 the Grants Processing Section was among the first B/I/D's at NIH to begin preparing the Notice of Grant Award for its research, training and fellowship programs by using its own computer terminal. By assuming this responsibility from the Division of Research Grants, the time needed to process awards has been reduced from 14 to 5 working days. The Notice of Grant Award can therefore be issued to the Principal Investigator and Grantee Institutions in an even more timely fashion than had previously been possible.

The Grants Management Branch is now responsible for coordinating responses to Freedom of Information (FOI) requests submitted to the NINCDS. In FY'82 the GMB will process an estimated 175 FOI requests. These requests will range from the simple, such as copies of the minutes of meetings which can be released generally without deletions, to the complex, such as summary statements, grant applications, etc., which can be released only after required deletions have been made for privacy purposes and patent issues are resolved.

ANNUAL REPORT
October 1, 1981, through September 30, 1982
Contracts Management Branch
Extramural Activities Program
National Institute of Neurological and
Communicative Disorders and Stroke

The Contracts Management Branch (CMB) consists of the Chief of the Branch, four specialists, and three supporting staff.

During fiscal year 1982, the CMB was responsible for some 85 contracts and interagency agreements, totaling $13 million in awards. The total value of these contracts, including amounts obligated to-date, is nearly $60 million. There are 22 ongoing intra- and interagency agreements, some of which are funded from other sources not included in the dollar amount above. In addition, there are some 90 research contracts that have expired and are in the process of being administratively closed out.

During fiscal year 1982, the CMB issued 11 Request for Proposals (RFPs) for the purpose of soliciting new contract projects and for recompeting several ongoing projects. It is expected that approximately 16 new contract awards will be made during the year due to anticipated multiawards as a result of more than one of these solicitations. Added to this workload are 45 renewals of existing contracts with additional funding and over 80 other actions modifying contracts in some manner but not requiring additional funding.

This year saw the introduction of a second utilization of the Master Agreement. The Master Agreement mechanism is being implemented to add flexibility to the Program areas and to speed the procurement process. By the end of FY 1982, it is anticipated that 15 Master Agreements for another Program will have been awarded.

Two members of the staff, Ms. D. Selleh and Ms. P. Davis, recieved Quality Step Increases during FY 1982. In a special ceremony Ms. Davis also received the NIH Award of Merit.

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Office of Data Analysis and Reports
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

Personnel Activities: Two grant clerks retired. A technical information specialist was hired to assist with disorder, scientific, and program area classification of grant applications and data activities. A clerk-typist was moved into a computer programmer trainee position. A new clerk was hired. Overall staff size is unchanged -- four program analysts, an accounting technician, a technical information specialist, two computer programmers, a computer programmer trainee, and a clerk-typist. Several staff members have attended training courses mostly in the automatic data-processing area. One employee was promoted; one received a quality step increase.

The office continues to publish a complete series of printed fiscal and currently active data books. These include, on an annual basis, the Training Data Book, the Fiscal Year Summary Book Series (four volumes), and on a semi-annual basis the Research Grants Data Book. Quarterly and Council reports are also produced though not sent to a printer.

During Fiscal Year 1982 ODAR implemented an automated system of tracking the payment of grants, replacing a manual ledger system that had existed for several years. It is operated and maintained by our accounting technician. The data base is updated daily; preprogrammed reports are available on demand.

ODAR also developed and implemented an automated system for tracking other object expenditures in the extramural programs. Our accounting technician, using input provided by the extramural administrative offices, also operates and maintains this data base. Data are input to this system the same day they are received from the administrative offices; preprogrammed reports are produced monthly or more frequently if necessary.

ODAR is now producing about 400 computer-generated letters each Council cycle, notifying principal investigators of Council actions. Formerly, this letter production required someone manning a mag-card machine for about 40 hours.

One of our routine responsibilities includes assigning disorder, scientific, program area, discipline specialty field, and the principal investigators' specialty codes to grant applications for reporting purposes. We process about 1,600 applications annually.

In addition to the above-mentioned activities, the Office of Data Analysis and Reports (ODAR) responded again to more than 300 requests for information not only from within the Institute, but also from other NIH Institutes and Federal and non-Federal agencies.

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Scientific Review Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Scientific Review Branch (SRB) is responsible for the technical merit review of applications for Research Program Projects, Specialized Centers, Workshops/Conferences, Teacher-Investigator Development Awards, and Institutional National Research Service Awards. The Branch has three standing Committees -- Communicative Disorders Review Committee (CDRC), Neurological Disorders Program Project Review A Committee (NSP-A), and Neurological Disorders Program Project Review B Committee (NSP-B). Although these three committees are responsible for the technical merit review of the majority of grant applications, it is necessary to convene a number of ad hoc committees to evaluate applications not assigned to a standing committee and to evaluate all contract proposals submitted in response to a "Request for Proposal."

On September 30, 1982 the staff of the Scientific Review Branch included the following individuals:

Ellen G. Archer, Executive Secretary, NSP-B
Mary Black, Clerk Typist
Alfred Bruner, Executive Secretary
Diane Casillas, Grants Technical Assistant
Margaret Caudle, Grants Technical Assistant
Leon J. Greenbaum, Jr., Executive Secretary, NSP-A
Frances Hisaoka, Grants Technical Assistant
Joyce Lamb, Grants Technical Assistant
Katherine Phillips, Grants Technical Assistant
Meigs L. Ranney, Lead Contracts/Grants Technical Assistant
Marilyn Semmes, Executive Secretary, CDRC
Raymond Summers, Chief
Howard Weinstein, Executive Secretary
Arthur B. White, Executive Secretary
Olga Williams, Grants Technical Assistant

The following table summarizes the number and type of grant applications that were reviewed and it indicates the number of site visits that were made.

NUMBER OF APPLICATIONS REVIEWED AND SITE VISIT MADE BY

SCIENTIFIC REVIEW BRANCH PERSONNEL ACCORDING TO TYPE OF APPLICATION

Type of Grant Application	Review by Standing NINCDS Committees (CDRC, NSP-A and NSP-B)	
	Number of Applications	Number of Site Visits
Program Project (P01)	47	41
Specialized Center (P50)	21	14
Cooperative Clinical Research Grant (R10/R01)	9	8
Conference Grant (R13)	11	0
Teacher-Investigator Development Award (K07)	54	0
Institutional National Research Service Award (T32)	33	0
TOTAL	175	63

The table shows that 175 grant applications were reviewed and that 63 site visits were made. It should be noted that the number of applications and number of site visits for applications going to the January 1982 Council has been estimated.

Concerning the technical merit review of contract proposals that were submitted in response to RFPs, 38 were received in response to 6 RFPs. Responses are due for two additional RFPs (82-08 and 82-09) before the end of the fiscal year and we do not know how many proposals will be received.

Personnel in the Scientific Review Branch work closely with all components of the Extramural Activities Program and with personnel in the five NINCDS programs. It is imperative that we maintain liaison with leaders of the scientific community for the purpose of identifying the most qualified individuals to serve on our technical merit review committees and panels.

TAB 3 -- COMMUNICATIVE DISORDERS PROGRAM -- CDP

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

TABLE OF CONTENTS

GRANTS ACTIVITY SUMMARY (continued)

CONTRACT NARRATIVES

PROJECT REPORTS (continued)

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

Introduction

The Communicative Disorders Program is concerned with the scientific bases of communication between individuals (speech, voice, hearing), with the scientific bases of the individual's communication with his or her environment (chemosenses, balance control) and with the disorders of those modes of communication. The normal physiology of many of these communication systems is poorly understood, and since, in many if not all instances, treatment or prevention of disorders is dependent upon a clear understanding of the normal, clinical management of disorders is often limited to symptomatic treatment or rehabilitation. The Program therefore encourages basic investigations of system physiology, and investigations directed to the application of basic knowledge in the prevention and treatment of disorders.

Communicative Disorders Program Staff

Ralph F. Naunton, M.D., F.A.C.S., Otolaryngologist, has served as Director of the Communicative Disorders Program during the past year.

J. Buckminster Ranney, Ph.D., has served as Deputy Director of the Program.

Earleen Elkins, Ph.D., Audiologist, directs the hearing portion of the Program and also supervises the Audiology Service at the Clinical Center, responsible for diagnostic clinical audiology and clinical research.

Christy L. Ludlow, Ph.D., Speech and Language Pathologist, directs the speech and language portions of the Program. In addition to her Extramural Activities, she maintains a clinical research program with the assistance of Ms. Celia Bassich, Research Speech Pathologist.

Ernest J. Moore, Ph.D., Audiologist, directs the vestibular, otolaryngologic and cochlear prosthesis portions of the Program.

Jack Pearl, Ph.D., Chemosensory Physiologist, is responsible for the chemosensory and haptic portions of the Program.

Ad hoc Advisory Committee Meetings

The Advisors have met on two occasions during the past year. Each of the following was present at one or both of these meetings:

Dr. Robert C. Bilger University of Illinois	Dr. Robert I. Kohut Bowman Gray School of Medicine
Dr. Norman Geschwind Beth Israel Hospital	Dr. Murray B. Sachs Johns Hopkins School of Medicine
Dr. Raymond D. Kent Boys Town Institute	Dr. David V. Smith University of Wyoming

Program staff also attended these meetings together with a number of other representatives from the Institute. The Advisors have provided direction to the Program bearing on future areas of research, in particular, identifying those calling for special emphasis. They have also critically evaluated staff suggestions for new or special initiatives, approving of them or suggesting modifications. The next meeting is scheduled for October 1982.

Program Activities

In collaboration with the Office of Scientific and Health Reports a booklet was developed and published on "Hearing Loss: Hope Through Research." It provides current information on hearing disorders and diseases and is designed for the lay public. (Dr. Elkins)

In order to encourage serious investigations of tinnitus, a Program Announcement was issued for studies which would address this very common complaint of hearing-impaired people. Applications are sought to define the auditory properties of tinnitus as well as the possible causes and treatment of this phenomenon. (Dr. Elkins)

Speech is used in a number of different ways to measure the hearing ability of a listener. A conference was held to explore current clinical procedures and to relate recent research findings to the improvement of diagnostic methods. The participants also determined future research that is required to evaluate peripheral and central processing of speech stimuli, - whether or not the patient requires the use of a hearing aid. (Dr. Elkins)

Efforts to improve information services for clinicians and investigators in the communicative sciences are continuing. The Communicative Disorders Program staff conducted an evaluation study of Deafness, Speech and Hearing Abstracts, the major abstracting periodical in the communicative sciences and disorders. They recommended upgrading this publication with the use of the MEDLINE data base of the National Library of Medicine. Consequently, an agreement was developed with the NLM to provide current citations for dsh Abstracts and CDP staff are developing the retrieval programs for each of the fields in the communicative sciences and disorders. The first issue using the expanded and timely data base provided by MEDLINE services will be published early in 1983. Since dsh Abstracts reviews

the world literature in deafness, speech, language and hearing, these efforts will have impact on the availability of recent research information for specialists in these fields. (Drs. Ludlow and Reiner)

The MEDLINE evaluation project is continuing as a national study of the needs of specialists in communicative sciences for improved information services. Over 700 professionals are participating in the study and are primarily speech-language pathologists, audiologists and graduate students. Very few have previously had exposure to computerized data bases; most were using individual journal subscriptions and discussions with peers to keep abreast of recent developments in their fields. Based on the first year of receiving MEDLINE services, it is becoming evident that users prefer accessing bibliographic information with the help of a technical information specialist with background training in communicative disorders rather than searching independently or having a search done for them. MEDLINE services seem most satisfactory for accessing information in subject areas beyond a user's particular specialty.

In 1982, a five year evaluation of performance in the speech and language research program was conducted by CDP staff. Since 1978, the number of speech and language grant applications received has doubled from 36 to 74 (105% increase). However, over the same time period, the number of speech and language applications funded has increased by only 29%. Between 1978 and 1982 the rate of approval of applications has increased from 64% to 73% while the percentage of approved grants which are funded has decreased from 57% to 35%. Hence, due to a shortage in funds in the Communicative Disorders Program, support has been unable to keep pace with the rapid growth and increase in quality in speech and language research applications over the last five years. An evaluation of program performance by mechanism reveals that funding has kept pace with inflation only in the support of research grants, even though it has not kept pace with growth in the number of applications received as indicated above. Between 1978 and 1981, the available dollars for research grant support increased by 31.4% over inflation. This was largely due to the competitiveness of the grant applications received in this area, since the increase in grant funding over inflation for the NINCDS as a whole over the same period was 23.4%. At the same time, contract research support has been reduced in actual dollars by 11.5% and when adjusted for inflation, this represents a reduction of 32% in real spending. This reduction has effected a decrease in programmatic efforts aimed at developing measurement and diagnostic tools for research in speech and language disorders for which the contract mechanism was being used effectively. Past accomplishments included the development of: treatment coding systems to quantify progress during language intervention; screening tests for early detection of delayed language development; a procedure for evaluating communicative abilities of aphasics, hearing impaired and aging adults; methods for diagnosis of sensory and perceptual disorders in language impaired children; and, methods for measuring hemispheric differences in cerebral metabolism in aphasic adults following stroke. The dollars spent on training new investigators in speech and language research have increased over inflation between 1978 and 1981 by 12.75%. However, when the number of trainees receiving support is examined across the 4 different training support programs during this time there are dramatic differences. Increases occurred in the two research career support programs; the number of Teacher Investigator Development Awards increased from two to seven while Research Career Development Awards increased from one to three. At the same time, however, the number of postdoctoral trainees decreased drastically in both the individual National Research Service Awards as well as Institutional NRSA support programs.

The total number of postdoctoral candidates was 27 in 1978 and only 10 in 1981, - a 63% reduction in the number of candidates being trained in research. The effects of these reductions will become most evident in the next five to ten years. (Dr. Ludlow)

Subsequent to the marked reductions in postdoctoral training in speech and language research a Program Announcement entitled, "Institutional National Research Service Awards for Clinical Research Training in Speech and Language Disorders" was issued in September 1981. Over 65 inquiries and 12 applications were received during the first 8 months of this announcement. It is expected that some increase in post-doctoral training in speech and language research will be effected in 1983 through this program. (Dr. Ludlow)

In order to encourage physician involvement in research directed towards the prevention and treatment of otolaryngologic communicative disorders, a Program Announcement was published encouraging the formation and application for support of Clinical Otolaryngologic Research Centers. These would comprise clinical and basic scientists working in collaboration towards the prevention and treatment of specific disease entities. Approximately 35 inquiries have been received by the Program to date. (Dr. Moore)

In collaboration with the Journal of the American Medical Association an article entitled, "Taste and Smell: The Neglected Senses" was published. This will provide information to the medical community on chemosensory disorders and type of preventive interventions available. (Dr. Pearl)

A Hearing, Language and Speech Voluntaries meeting was held in April 1982. Invited representatives from ten (10) voluntary associations, councils, foundations or institutes met to share perceptions and needs for hearing, language and speech research. Three complementary themes were identified by the participants: Indentification, Intervention and Prevention. Observers from other voluntary associations attended the meeting as well as observers from professional associations. (Dr. Ranney)

Staff Presentations at National and International Meetings

Bassich CJ, Ludlow CL. "The use of perceptual methods for assessing vocal pathology." American Speech-Language-Hearing Association.

Elkins E, Pikus A. "Audiologic Profile in Peripheral Neurofibromatosis." American Speech-Language-Hearing Association.

Elkins E. "NIH Support for Research in the Communicative Disorders." National Council of Graduate Departments of Psychology.

Elkins E. "NIH Clinical Research in Hearing." National Conference on Research Goals and Methods for Otolaryngology.

Elkins E, Dolan TR. "Review and Funding of Research Grants Pertaining to Hearing at NIH and NSF." Acoustical Society of America.

Ludlow CL. "Objective measures for assessing speech impairments in dysarthria." American Speech-Language-Hearing Association.

Ludlow CL, Bassich CJ. "The results of perceptual and acoustic assessment of two types of dysarthria." Clinical Dysarthria Conference.

Ludlow CL, Insel TR, Bassich CJ. "Oral expressive language elicitation deficits in obsessive-compulsive adults." International Neuropsychological Society.

Ludlow CL. "The brain bases for language functioning: New insights from penetrating head injuries." Georgetown University Round Table on Languages and Linguistics, "Contemporary Perceptions of Language: Interdisciplinary Dimensions."

Ludlow CL. "Identification and assessment of aphasic patients for language intervention." National Conference on Language Intervention.

Ludlow CL, Rosenberg J, Dillon D, Buck D. "Persistent speech dysprosody following penetrating head injuries." Speech Motor Control Conference.

Ludlow CL, Cudahy EA, Bassich CJ. "Developmental, age and sex effects on gap detection and temporal order." Acoustical Society of America.

Ludlow CL, Coulter DC, Bassich CJ. "Relationships between vocal jitter, age, sex and smoking." Acoustical Society of America.

Ludlow CL, Coulter DC, Gentges F. "The effects of changes in vocal fold morphology on phonatory jitter." Voice Foundation Symposium: Care of the Professional Voice, Juilliard School.

Moore EJ. Chairperson for session on Speech, Language and Audiological Services at the American Speech-Language-Hearing Association meeting.

Moore EJ. "Bases of Auditory Brain Stem Evoked Responses." National Black Association of Speech, Language and Hearing.

Naunton RF. "Funding for Research in Communicative Disorders." Society of University Otolaryngologists.

Naunton RF. "Research in Otolaryngology: NIH Support and Other Considerations." Middle Section of the American Laryngological, Rhinological and Otological Society.

Naunton RF. "Preparation of Research Grant Applications." Association for Research in Otolaryngology.

Naunton RF. "The Communicative Disorders Program." National Conference on Research Goals and Methods in Otolaryngology.

Pearl J. "NIH Support for Taste and Smell: Research and Training." Association for Chemoreception Sciences.

Ranney JB. "Deafness Research Opportunities." International Convention of the Alexander Graham Bell Association for the Deaf.

Reiner BJ. Exhibit on the Use of MEDLINE for Bibliographic Retrieval in Communicative disorders. American Speech-Language-Hearing Association.

Staff Presentations at Other Meetings

Elkins E. "Federal Grants." American Speech-Language-Hearing Association.

Elkins E. "Federal Support of Research of the Hearing and Vestibular Systems as Reported for FY 1979 and FY 1980." Committee on Hearing, Bioacoustics and Biomechanics, National Academy of Sciences.

Elkins E. "Statistical Procedures for Analyzing Speech and Hearing Research." Seminar for Advanced Studies, University of Maryland.

Elkins E. "Speech Recognition and Hearing Aids: 1982 State of the Art." Maryland Speech-Language-Hearing Association.

Elkins E. "Experimental Design and Analysis of Auditory Evoked Response Data from Adult Subjects." Washington Hospital Center, Washington, D.C.

Elkins E. "Noise-Induced Hearing Loss." D.C. Chapter of Graduate Women in Science.

Moore EJ. "Grants and Contracts." Grantsmanship Workshop, Howard University.

Moore EJ. "Rules and Procedures for Applications to NIH." Universities of Goteborg, Karolinska, Upsalla and Malmo, Sweden.

Moore EJ. "Auditory BSER: Stimulus Parameters and Clinical Applications." Universities of Goteborg, Karolinska, Upsalla and Malmo, Sweden.

Naunton RF. "The Hearing Impaired Child." Keynote Address. Illinois Department of Public Health Symposium.

Pearl J. "NIH Support of Chemosensory Research." Monell Chemical Senses Center.

Other Staff Activities

Dr. Elkins:

- Served as Institute representative to the Committee on Hearing, Bioacoustics and Biomechanics; National Academy of Sciences. (Member of Tinnitus and Auditory Evoked Response Working Groups).

- Served as chairperson, Committee on Speech Audiometry, American Speech-Language-Hearing Association.

- Served as member, Committee on Speech Recognition, Acoustical Society of America.

- Served as consultant, Audiometric and Tympanometric Data Collection and Analysis, National Health Examination Survey, National Center for Health Statistics.

- Served as member, Advisory Board for NASA/Gallaudet College project: Autocuer Device for the Hearing-Impaired.

- Served as member, Committee on Research Facilitation, National Conference on Research Goals and Methods in Otolaryngology.

Drs. Ludlow and Reiner:

- Served as consultants to the Executive Board, Deafness, Speech and Hearing Abstracts.

Dr. Ludlow:

- Served as member, Consortium of Affiliates for International Programs of the American Association for the Advancement of Science.

- Served as chairman, Scientific Affairs Committee of the American Speech-Language-Hearing Association.

- Served as chairman, Journal Selection Committee, Deafness, Speech and Hearing Abstracts.

- Served as Liaison Representative to the American Speech-Language-Hearing Association to the American Association for the Advancement of Science.

- Served as member, Speech Communication Technical Committee, Acoustical Society of America.

- Served as Associate Editor (Neuropathologies), Journal of Speech and Hearing Research.

- Served as member, Editorial Advisory Board, Journal of Developmental and Behavioral Pediatrics.

- Appointed principal investigator of speech and language research on the Vietnam Head Injury Program funded by the Veterans Administration and supported by the Army, Navy and Air Force.

- Elected to membership in the Academy of Aphasia.

- Appointed member, Speech Communication Technical Committee, Acoustical Society of America.

Dr. Moore:

- Served as NIH Tour coordinator, National Conference on Research Goals and Methods in Otolaryngology, Bethesda, Maryland.

Dr. Naunton:

- Served as chairman, Membership and Credentials Committee, American Neurotology Society.

- Served as member, Editoral Board, American Journal of Otolaryngology.

- Served as President, American Auditory Society.

- Served as member, American National Standards Institute (Bioacoustics).

- Served as consultant, ENT Devices Section, FDA Panel on Dental, Ophthalmological and ENT Devices.

- Served as member, Board of Directors, Better Hearing Institute.

- Served as member, Committee on Research, American Otological Society.

- Appointed Honorary member, Society of University Otolaryngologists.

- Presented listener call-in program on Tinnitus, WAMU Radio, Washington, D.C.

Dr. Pearl:

- Served as member, NINCDS Equal Employment Opportunity advisory committee.

- Serving as CDP representative, NINCDS Symposium on Pain Measurement and Assessment.

- Discussed disorders of taste and smell, radio program.

- Manned Institute exhibit at Association for Chemoreception Sciences.

Dr. Ranney:

- Represented CDP/NINCDS at the Interagency Ad Hoc Committee on Deafness/ Hearing Impairment Research meetings, Washington, D.C.

- Served as chairman for the Scientific Exhibits Sub-Committee for the 1982 American Speech-Language-Hearing Association Program Committee.

- Served as member, Committee on the Clinical Fellowship Years, American Speech-Language-Hearing Association.

Clinical Activities

Dr. Elkins

Clinical research in hearing, under the direction of Dr. Elkins and in cooperation with Ms. Pikus and Ms. Grimes of the Clinical Center, continues to focus on hearing losses associated with various diseases and disorders. Studies are being conducted to identify carrier status in selected genetic diseases; detect ototoxicity related to chemotherapeutic agents and radiation therapy; document suspected hearing impairment associated with several neurological disorders; develop a profile of risk factors for presbycusis; and develop techniques for the measurement of auditory function in autistic children and adults. Hearing and middle ear function in Osteogenesis Imperfecta resulted in a publication in cooperation with investigators in the Clinical Center and the Division of Computer Research and Technology. This study showed that a majority of the subjects (N=55) display absent acoustic reflexes and increased compliance of the middle ear with notched tympanograms suggestive of anomalous ossicular articulation. Similar findings in otherwise uninvolved relatives (N=92) suggest a genetic basis for these defects. Details of other studies in progress may be found in the reports of research projects.

Dr. Ludlow

Outpatient clinical research activities have increased to accommodate ongoing speech and language research protocols under the direction of Dr. Ludlow. These protocols are being conducted in collaboration with otolaryngological services in the Clinical Center. Referrals of chronic undiagnosed laryngeal disorders are being received from local and national sources. Patients are participating in diagnostic studies of several phonatory disorders including spastic dysphonia and aphonia. New procedures for predicting the effects of recurrent laryngeal nerve section in patients with spastic dysphonia are being developed and have potential for use in differential diagnosis of these disorders.

An automated system for measuring vibratory function during phonation for speech is being used in assessment of phonatory abnormalities associated with changes in vocal fold morphology. One measure is particularly sensitive to structural asymmetries between the vocal folds and will identify when small growths occur on one of the vocal folds such as in laryngeal carcinoma, polyps or nodules. This analytic technique has potential for clinical application since it appears to be insensitive to symmetric morphological changes in the vocal folds such as are associated with smoking or age.

An acoustic analysis system containing many parameters for analyzing dysarthria speech was completed and received well by the scientific community. It is valid for differentiating (a) between normal and dysarthric speech and (b) between speech symptoms associated with pathologies involving different structures within the central nervous system. The successful completion of this analytic system will allow investigations into the organization of the speech motor control system as reflected by brain lesions and neuropathologies at specific locations in the CNS. Speech motor disturbances in tardive dyskinesia, Parkinson's disease, Huntington's chorea, and dystonia are being evaluated to determine whether the measures developed are sensitive to differences in neuropharmacological intervention and could be useful in treatment research.

Experiments involving oral and speech motor control in tardive dyskinesia and Huntington's disease are aimed at determining whether lip and jaw movement range and rate are affected when undisturbed by the intrusion of involuntary movements. A unique three dimensional movement transducer for lip and jaw movements was developed for this research to measure lip and jaw movement displacement, velocity and acceleration during automatic, purposive and speech movements. The purpose of this research is to determine how speech movement patterning is disturbed by pathology at the level of the basal ganglia.

The speech and language research program is using some of the above techniques in the study of speech motor control in penetrating head injuries in collaboration with the Vietnam Head Injury Study at Walter Reed Army Medical Center. CT scanning is being used to quantify the extent and location of central nervous system damage. Experimental studies of speech motor control in patients with well defined lesions at different brain locations will ascertain which structures are critical to the integrity of speech motor control. Since these penetrating lesions have different locations from those associated with cerebrovascular accidents, the findings thus far provide critical new tests of hypotheses regarding neural organization of speech programming. A syndrome of residual speech dysprosody 10 or more years following brain injuries has indicated that frontal lobe white matter tracts from the pars opercularis on either the left or right side have importance in the control of rate of sequential movements in speech. Further, residual Broca's aphasia 10 or more years following brain injury has been found only when fronto-parietal white matter tracts from the Rolandic fissure and pre-motor regions are completely involved, rather than Broca's region.

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Speech and Language

Basic Studies

Speech production research is aimed at understanding how humans plan and execute speech, by examining to what degree the movement patterns for producing speech sounds are fixed motor programs in adult speakers. When adults were instructed to increase or decrease their speaking rate, the timing of muscle contractions and articulator movements for the production of consonant sounds were invariant relative to the length of vowel productions. Thus, constant time relationships are maintained between different articulator movements for speech sounds regardless of the speaker's overall speech rate suggesting that speech production is programmed in units containing all the movements required for producing consonants and vowels together. Further examination of these issues includes studies of coarticulation, the influence of the movements required for one speech sound upon preceding sounds. Electromyographic studies of vowels requiring lip rounding determined that the movement gesture associated with the vowel is initiated at a fixed time preceding the vowel regardless of the types of sounds preceding the vowel. These results suggest that each speech sound is preprogrammed as a motor gesture and not dependent upon which sounds precede or follow it.

Animal studies of the organization of laryngeal motor neurons in the brain stem are aimed at determining the neural control of individual motor units in the larynx. The location and morphology of cell bodies which control motor units involved in vocal fold adduction and abduction for sound production, inspiratory gestures of the larynx and airway protection mechanisms such as coughing, are being studied in monkeys. Determination of whether the same neurons contribute to different functions and are recruited to varying degrees for different functions will provide new knowledge regarding the neural control of the larynx. Stimulation studies of single motoneuron axons in the brain stem of anesthetized monkeys have demonstrated both expiratory and inspiratory motor units in the cricothyroid. The expiratory units have faster conducting axons and faster contracting muscle fibers than the inspiratory units and are derecruited during elevated PCO_2 or inspiratory dyspnea. The cell bodies for these units were found in the dorsal subdivision of the nucleus ambiguous. Inspiratory units were recruited during PCO_2 or forced inspiration. Similar studies will determine whether the same motor units have separate functions for vocalization and are controlled by the same brainstem nuclei.

Speech perception studies of man's ability to recognize speech sounds, have increased dramatically in recent years. Recent research has indicated that the process is much more complicated than was originally thought. Acoustic spectra with the same frequency components as natural speech but containing sinusoidal replicas are perceived differently by listeners dependent upon whether they are told that they will be hearing sound or speech, suggesting that adult listeners use different perceptual mechanisms for perceiving speech and non-speech sounds. Investigators are currently producing synthetic speech stimuli and varying the acoustic cues to determine what normal adult listeners require to be able to perceive phonetic segments.

Neuropsychological studies of the degree of lateralization of language functions have demonstrated differences between normal left and right-handed subjects in the laterality of language functions. Over 300 male and female left-handers and 250 right-handers have been administered an extensive battery of tests of the laterality of language and non-language functions including dichotic listening, finger tapping with concurrent naming and reading, manual preference, eyedness, manual dexterity, handwriting posture, familial handedness, figure-ground perception and manual and pedal asymmetries. The data have consistently indicated a different, more variable, bilateral brain organization for language functions in left handers in comparison with right handers.

The influence of sex on differences in brain organization for language have also been examined in this research. No support has been found for the hypothesis that there are language lateralization differences between males and females.

Causal and Predictive Factors in Disorders

The major obstacle to effective prevention or treatment of many speech and language disorders is the lack of knowledge regarding the cause of the disorder. Examples of this are language and learning disorders in children. Brains of individuals known to have had specific language learning disorders such as dyslexia are being obtained for postmortem study of the cellular structures in the brain. Previous neuroanatomical studies of adult, fetal and infant brains have demonstrated lateral asymmetries, with regions of the left temporal lobe being greater than on the right. Scientists have postulated that the lateralization of language in the left hemisphere in 98% of persons may, therefore, have a neuroanatomical basis. Cytoarchitectonic studies of cellular organization in adult brains have demonstrated that particular regions in the temporal lobe contain the cells specific to the region in greater numbers on the left side. Possibly during brain development a greater number of cells migrate to the left than to the right lobes. A recent cytoarchitectonic study of a dyslexic brain demonstrated an abnormal cellular organization of the left temporal lobe suggesting that abnormal cell migration patterns during brain development may underlie some of these congenital disorders.

Human geneticists are examining the family histories of stutterers and have found a significantly greater family history of stuttering in stutterers than that found in fluent speakers. Genetic linkage studies are proceeding in families with a high density of stuttering over several generations in an effort to identify loci which may have an association with the occurrence of stuttering in these families. The identification of genetic mechanisms which may underlie the development of abnormal brain mechanisms responsible for congenital speech and language disorders has potential for the prevention of such disorders as stuttering, developmental language disorders and dyslexia.

Investigators are validating a predictive screening test which can be administered to pre-schoolers and first graders to identify those children who are at risk for developing dyslexia on learning to read. Rapid automated naming tests were administered to 300 children between five and six years of age along with tests of language comprehension, non-verbal cognition and lateral dominance for language. These children are being followed as they undergo reading training to

determine which children later have dyslexia. It is hoped that particular patterns of fluency and poor rhythmicity on rapid naming prior to reading will be predictive of reading failure in schooling. If so, children at risk for developing dyslexia can be identified early and effective intervention provided to prevent the appearance of reading problems in school.

Diagnosis, Treatment and Rehabilitation

Experimental investigations are comparing the language learning characteristics of language impaired children with normal children who are at the equivalent stages in language development, and therefore much younger than the language impaired group. In both groups the acquisition of new words for production is poor when the words contain speech sounds the subject has not yet acquired. Thus phonological development appears to play a significant role in language development and should be focused on in language intervention.

Further, a study of the effects of participating in imitation was examined relative to the acquisition of new words. Speech imitation was not beneficial to language impaired children in an attempt to improve their production of new words. This finding contra-indicates the use of speech imitation in intervention--a technique now employed by many clinicians.

Research on the diagnosis and treatment of patients with spastic dysphonia has continued. The recent discovery of the effectiveness of cutting one of the recurrent laryngeal nerves to the vocal folds continues to be difficult to explain. Continued comparisons of segments of the recurrent laryngeal nerve of patients with spastic dysphonia and normals using light and electron microscopy yield no significant differences, suggesting that the basis for the disorder is more central. Diagnostic techniques which are predictive of the outcome of recurrent laryngeal nerve section treatment for spastic dysphonia are currently being explored. Laryngoscopy, aerodynamics, acoustics and laryngography have not been found useful in the diagnosis of spastic dysphonia. Rather, clinical phonatory characteristics seem most predictive. Vocal arrests and vocal tremor have been found to be distinct entities with vocal tremor predictive of little benefit from recurrent laryngeal nerve surgery. A new technique of using a CO_2 laser for thinning the body of the paralyzed vocal fold has been found effective in treatment of those cases in which spasticity recurs.

New treatment techniques for aphasic adults following stroke are being developed. Lesion sites observed on CT scans have been found predictive of the outcome of Melodic Intonation Therapy with non-fluent chronic aphasic patients. Those with a good response to treatment had lesions primarily associated with either Broca's area (cortical) or capsular/putamenal regions with anterior/superior lesion extension (subcortical). The CT scan lesion sites of poor treatment responders were either bilateral, or unilateral with lesions including Wernicke's area (cortical) or in the auditory radiations in the temporal isthmus (subcortical).

Communicative aids are being developed for several groups of patients who are non-vocal and severely physically disabled and have no means of communication with others. Often such patients only have control remaining for eye movement such as in the terminal stages of Amyotrophic Lateral Sclerosis. An ocular control device has been found useful for such patients. The device fits on the patient as a pair of eye glasses and tracks eye movement. Training the patient

to use the device requires a minimum of two 30 minute sessions. The patient can use the device to control other aids or to communicate through synthetic speech. This and similar communicative devices are allowing such patients to escape from their "locked in" condition and make their needs and thoughts known.

Taste and Smell

Basic Studies

Understanding the trophic maintenance and regeneration of receptor cells is important in attempting to prevent degeneration and aid recovery of impaired neural systems. The olfactory system is unique in that the first-order neuron is capable of regeneration, spontaneously and after insult such as bulbectomy, axonal damage, or treatment of the olfactory epithelium with $ZnSO_4$. The olfactory bulbs are not required for the acquisition of olfactory tasks by mice. After bilateral bulbectomy, discrimination was lost, but returned with the formation of synaptic connections between regenerated olfactory receptor cells and the cortex of the forebrain. It is not known whether the regenerated system has the same sensitivity and range of responsiveness to odor as the undamaged system. Results in hamsters suggest that receptor density, but not the total number of receptors, reaches control levels after regeneration. The replacement of receptors occurs in a thinner sheet of epithelium.

The electro-olfactogram (EOG) records the slow negative potential developed at the surface of the olfactory epithelium. Results suggest that the EOG reflects primarily the activity of young receptor cells that are not connected to the olfactory bulb. Results in frogs showed a correlation between the rate and the amplitude of the EOG and the rate of the regrowth of olfactory cilia during the recovery from the insult of $ZnSO_4$.

Because of its length, the garfish olfactory nerve is an ideal preparation for studying certain aspects of axonal transport and degeneration. When crushed, this nerve degenerates from the crush site toward the synapse. The rate of degeneration decreases linearly with temperature. Since the rates of degeneration are identical to the slow phase of axonal transport in regenerating fibers, it is hypothesized that slow flow is taking place in the axons that have been separated from their cell bodies. This slow flow would eventually cease because the cell bodies cannot replenish the flow and the cessation of flow would induce degeneration of the axons.

The taste buds also regenerate. Previous work with adult rats showed that bilateral glossopharyngeal nerve denervation produces a loss of all the vallate taste buds, whereas unilateral denervation produces a loss of about only 10% of the buds because of the bilateral innervation of the buds. Studies in rat pups show that unilateral denervation prevents many of the buds from developing and suggests that interaction between fibers and bud precursors must occur during early development to induce the normal number of buds.

Structure and Function

It may be necessary to revise the concept of the human olfactory epithelium to include two morphologically distinct populations of receptor cells. One is the well-known ciliated type. The presumptive new one is a microvilli type. These

cells are being obtained with a recently developed tool that permits safe removal of small biopsies of olfactory mucosa from people.

The first example of competitive inhibition of sweet taste in mammals has been reported and results suggest that there are two types of receptor sites, a sugar and a non-sugar site on the taste receptor cells of gerbils. Electrophysiological results showed that a galactopyranoside did not stimulate the receptor, but inhibited the response to sweetness. Sugars were inhibited competitively; artificial sweeteners were inhibited non-competitively.

Causal and Predictive Factors in Disorders

Patients entering the clinical chemosensory centers include those with Kallmann's syndrome, in which the olfactory bulbs fail to develop, familial dysautonomia, in which certain taste buds fail to develop, and genetically-determined metabolic disorders. It is being shown that the inherited ability to fully taste the bitterness of phenylthiocarbamide is also associated with a greater ability to perceive sweets and other taste qualities. There are some indications that the tasters may be specially sensitive to certain chemotherapies. The chemical senses lend themselves to description in terms of molecular properties. There are olfactory studies whose results are being linked to immunological-like models where one part of the genetic locus of the major histocompatability complex is related to the chemical signal and another part is related to the reception of the signal.

The ability to detect the odor of a putative pheromone, androstenone, appears to be genetically determined as indicated by results with identical and fraternal twins and siblings. These results were not related to the expression of the major histocompatability complex.

The precise nature and causes of genetic variants in chemosensitivity in mice is being determined in psychophysical studies and electrophysiological investigations of nerve preparations for tastants.

There is concern about whether early experience with NaCl affects subsequent Na or water intake and hypertension. Pregnant rats were fed a Na-free diet from three days after gestation to twelve days after parturition. Their pups exhibited a decreased preference for salt solutions as opposed to water but drank more water and salt solutions than control pups. The difference in water intake between the two groups can account for their preferences. Peripheral responses from the chorda tympani were unremarkable when the salt-depleted pups were 24 days old.

Diagnosis, Treatment and Rehabilitation

Teams at two clinical chemosensory research centers are determining the advantages and limitations of different tests for evaluating the chemical senses in a standardized way in clinical settings. Psychophysical measurements include detection, recognition, identification and magnitude estimates of chemicals. A refinement is cross-modality matching in which a decibel equivalent is determined for salty, sour, sweet, and bitter tastants.

The interruption of the inhalation reflex by the inhalation of irritants through the nose may prove to be an objective index of the status of the common chemical sense. In comparison to non-smokers, smokers had a higher threshold for the reflex and judged the pungency of two selected odorants as less intense. Smoking during testing inhibited the inhalation reflex.

Measurement of chemosensory abilities offers opportunities for non-invasive detection of major disorders. For example, it seems possible to identify a subgroup of people who are genetically predisposed to insulin-dependent diabetes mellitus based on their perception of the taste of glucose. The intensity function for the prediabetics resembled that for recruitment in that sensitivity was poor at weak but normal at high concentrations. The prediabetics perceived fructose normally. The recruitment of the prediabetics for glucose suggests that there may be a separate receptor site with which glucose but not fructose interacts.

It is controversial whether zinc is effective in the treatment of chemosensory disorders. The mean plasma and red blood cell zinc levels of patients with chemosensory disorders were within normal limits. The levels in subgroups of patients are being analyzed.

Most of the hyposmics and anosmics who have entered one of the clinical chemosensory research centers appear to have nasal obstruction rather than disruption of neural function. The medical status of the patients included a history of polyps, allergic rhinitis, and periodic remission of symptoms. Viral infections and nasal obstruction are two of the common medical conditions which are associated with the olfactory disorders of patients who are entering another clinical chemosensory research center.

Children with nasal obstruction exhibited deficient detection thresholds for odorants. Associated medical conditions included adenoid hypertrophy, allergic rhinitis, and upper respiratory infections. Adenoidectomy enhanced olfactory sensitivity in many of the children with adenoid hypertrophy.

Touch

Basic Studies

There has hitherto been near-consensus that active touch leads to better performance than passive touch. This view is being increasingly challenged by new studies and reinterpretation of previous results. It was commonly believed that the scanned mode led to better performance than the static mode when letters were identified by the Optacon, an optical to tactile conversion instrument for the deaf-blind. Recent results challenge this view. It is still uncertain whether modes other than the scanned mode can improve real reading performance with the Optacon. One implication is that the different ways of generating tactile patterns need to be examined in the context in which they are used, whether for reading aids, mobility aids, or speech perception.

The principles of sensory coding of spatial information are being determined by examining somatosensory system integration of inputs from multiple points on the skin. Cutaneous sensation magnitude, measured by reaction time, was augmented in monkeys and people by increasing the number of stimuli points. Electrophysiological recordings from the cortex of monkeys support the hypothesis that there are large overlapping representations of the hand and arm rather than separate and distinct representations. Direction-sensitive responses in the cortex were obtained from punctuate and brush-like stimulation of the skin.

The study of sensory interactions is a natural approach to prosthesis studies. One of the ways to improve two-point tactile acuity is to add sensory information for temperature. This work is being extended to include interactions between

skin temperature and pressure sensation. Results of pilot studies on thermal-taste interactions suggest that the popularity of chile pepper could stem from its enhancement of the flavor of foods, including salty and sweet ones. It is known that the amount of sugar people use in their coffee depends on the temperature of the coffee. Recent results suggest that for some sugars the temperature effect may be linked to the nervous system of the person and for other sugars, to the mutorotation of their isomers in solution.

It is of clinical importance to know whether a skin graft may assume the characteristics of the donor or the recipient site. The temporal nature of sensory recovery is being measured with modern psychophysical tests and instrumentation and consideration is being given to physical metrics. Von Frey hairs yielded unreliable results. Measurement of the depth of skin indentation is proving to be more closely related to the intensity of tactile sensation than measurement of force.

Hearing

General Considerations

The division of the nervous system specialized for the processing of sound is called the auditory system. The structures outside the brain or brain stem are classified as peripheral and include the outer, middle and inner ear. The remainder of the system is known as the central auditory system and consists of an ascending pathway, a descending pathway and multiple interconnections between them. The more central portions of the system are less well understood than the peripheral portions. Knowledge of the auditory system has progressed from the periphery toward the cortex. Despite our incomplete knowledge of its function, from working with the hearing-impaired population it is known that major malfunctions of the system usually are associated with failure of the various mechanisms which process sound from the outer ear to the auditory portion of the cerebral cortex.

Peripheral Auditory System

Basic Studies

The major function of the middle ear is one of matching the acoustical impedance of air to the acoustical impedance of the fluid within the cochlea. This function is accomplished by a sound pressure transformation. A method has been developed which incorporates a high impedance acoustic source with a computer-controlled system for sound generation and measurement. Both magnitude and angle of acoustic admittance can now be measured over the broad frequency range of 10 Hz to 20,000 Hz. This work suggests that the effects of middle-ear cavities can be related to the anatomical dimensions of the cavities and that the admittance is primarily determined by the tympanic membrane at frequencies about 4,000 Hz. Further study indicates that two-tone distortion products and non-linear properties of the input admittance, indicate that some of the non-linear behavior that occurs for stimulus levels above 80 dB sound pressure level (SPL) results from mechanical properties of the basilar membrane.

The sensory receptor cells (hair cells), for hearing are located within the cochlea which in turn is embedded within the petrous portion of the temporal bone of the skull. The cochlea represents the first stage for processing sound in the auditory

system. It is a highly specialized end organ and a very sensitive one. Many studies are directed toward understanding the transformation of mechanical events to neural patterns in the cochlea by electrical or chemical phenomena.

Central issues in the study of the auditory periphery concern the role of inner and outer hair cells, by defining the nature of their population-specific responses and determining how their inputs are distributed to component divisions and neural populations within divisions of the cochlear nucleus. Studies show that the outer hair cell system projects to the brainstem and the axons of Type II neurons are present in the cochlear nerve at its entrance to the brainstem.

The transduction mechanism of hair cells is one of the least understood aspects of the hearing process. Studies show that outer hair cells are almost entirely responsible for the generation of cochlear potentials, but it is not known whether these potentials play an important role in the process of excitation of afferent fibers, most of which innervate the inner hair cells.

Another finding demonstrates that the receptor-potential responses of hair cells to tone-burst stimuli show frequency selectivity, non-linear properties and lowpass filtering. The frequency selectivity is sharper than that of the basilar membrane displacement, but roughly equivalent to the frequency selectivity of cochlear nerve fibers. Thus, sharp frequency selectivity is a property of individual hair cells. Non-linearities in hair cell responses occur at low sound pressure levels where the macromechanical properties of the middle and inner ear are linear.

Causal and Predictive Factors in Disorders

Past work has shown that the high metabolism of the cochlea makes it susceptible to agents in the blood stream such as drugs. The highly deleterious effects of the aminoglycosides and some other antibiotics are now well-known. However, the interaction of these drugs with loop inhibiting diuretics has only recently been under investigation.

If the molecular mechanism of ototoxicity is known, then the sites on the antibiotic that are responsible for this toxicity can be determined. Experiments are being conducted to modify the chemical composition of existing antibiotics to render them less ototoxic while still retaining their antibacterial properties.

Cochlear injury caused by noise exposure continues to attract the efforts of several investigators. One group has shown that interruptions in noise exposure of the same total acoustic energy will partially protect the low-frequency region of the organ of Corti, but not the more basal or high-frequency region. As a result of such work, it is felt that different kinds of lesions may reflect different mechanisms of acoustic injury.

Experiments in which a single exposure to noise was interrupted by inserting quiet periods, show that although hearing damage is not eliminated completely, it is significantly reduced by these recovery periods. This limitation of the total-energy principle is under study at intensities somewhat below the critical intensity. Present results indicate that when exposures are interrupted, the total energy may be as high as ten times as great as an uninterrupted one without producing a greater hearing loss.

Studies of the possible potentiation of noise exposure by common drugs such as aspirin are underway. Interestingly, aspirin is the only known pharmaceutical agent which is ototoxic during the drug regimen but whose effects are reversible once drug administration is discontinued.

Studies of the normal effects of aging on both the peripheral and brainstem portions of the auditory system are being compared with results obtained from animals with genetically-determined anomalies. This work is designed to separate genetic and aging effects to identify key factors responsible for the respective auditory impairments. Improved treatment of such patients is expected to result from this work.

Studies are being conducted to identify the etiology of idiopathic sudden hearing loss. By studying viral antibodies, attempts are being made to determine which viral agents are likely to be responsible for the hearing loss incurred by these patients. Current findings of work regarding the mechanisms of viral pathogenesis indicate that the reactivation of latent herpes viruses may play an important role. The pathophysiological mechanisms of diabetes, atherosclerosis, hypertension, hereditary and environmental factors are under study for possible association with sensorineural hearing loss.

The study of temporal bones from patients with documented Meniere's disease indicates that in Meniere's attacks, the permeability of the membranous walls of the labyrinth is altered. The tectorial membrane, and possibly the cupula also, shrink under the influence of an increased sodium concentration of the endolymph. The hydrostatic pressure of the endolymph also increases and tends to flatten the tectorial membrane against the reticular lamina. Changes in the tectorial membrane may be responsible for auditory dysfunction in Meniere's disease and in fluctuating hearing loss.

Humans with identical abnormal hearing threshold levels display large differences in performance on other auditory tasks. It has also been found that physiological damage to the auditory systems of experimental animals can be produced by moderate exposures to noise or ototoxic drugs without a concomitant measurable change in hearing threshold levels at conventional audiometric frequencies. Confirmation of this finding was obtained by exposing animals to either moderate amounts of noise or ototoxic drugs and then measuring their threshold levels, whole-nerve action potentials, the locus of tips of individual-nerve-fiber tuning curves and charts of hair cell destruction as a function of position along the basilar membrain. The only measure which showed any significant relationship with the pattern of hair cell loss was the tuning-curve measures. Although the other estimates of threshold agreed quite well with each other, all failed to reflect even rather large areas of destroyed hair cells.

Diagnosis, Treatment and Rehabilitation

Information about the basic mechanisms of hair cell function and the factors influencing the production of neural responses, are being pursued to develop, evaluate and improve techniques used for clinical diagnosis and treatment of human hearing disorders.

In order to develop prostheses for the severely hearing-impaired such as cochlear implants and tactile stimulators, it is increasingly important to understand neural saturation so that channel capacity will not be wasted by presenting

unencoded stimulation. Several experiments are providing information about the capacity of the auditory system to process stimuli with different parameters to separate normal performance from performance by listeners with moderate to severe hearing losses.

Ongoing studies are testing various aspects of theories of hearing to improve current models of cochlear function and provide insight into the process of acoustic information coding in the cochlea. One investigator is determining the processes involved in the coding of the temporal characteristics of low-and medium-frequency pure tones to achieve a better understanding of how more complex acoustic stimuli such as speech are coded and processed by the nervous system.

One of the difficulties encountered by researchers studying presbycusis is in differentially diagnosing it from noise-induced and drug-induced hearing loss. A unique opportunity to study inner ear changes associated with presbycusis in aging monkeys was presented when the temporal bones from a colony of 15 animals were obtained. The animals had not been exposed to either noise or ototoxic drugs and had well-documented premortem hearing assessments. Preliminary findings suggest that presbycusis is an independent phenomenon separate from the confounding factors experienced in the environment. Hair cell loss in the cochlea is being examined to support these conclusions.

Another problem which is thought to have its origin in the cochlea is tinnitus (ringing in the ears). At the present time, it is considered to be a symptom of a deeper underlying malfunction such as drug and noise toxicity, though it is reported as accompanying many other types of sensorineural hearing impairments. Few controlled experiments have studied the phenomenon of tinnitus because the most prevalent type, subjective, is perceived only by the sufferer and is difficult to quantify objectively. A recent study attempted to quantify the annoyance of tinnitus in patients with noise-induced hearing loss. The intensity of noise required to adequately mask their tinnitus had to be increased by more than 40 dB but changed significantly over time and probably indicates that the rate of fluctuation may be an important factor in determining the annoyance of tinnitus. Other studies are employing masking by narrow bands of noise as a means of relieving the tinnitus annoyance.

Treatment for people with sensory hearing losses is generally limited to wearing a hearing aid which in its basic form is a complete miniature sound system. Besides providing louder sounds for the hearing-impaired, clinicians are also concerned about protecting these listeners from excessively high level speech and environmental sounds. Researchers have been able to alter the hearing aid circuitry to compress loud incoming sounds but still preserve understanding of speech by these patients. Another research team is exploring ways to improve hearing aid amplification in reverberant environments which are known to create severe hearing problems for older persons. Other studies are employing various psychophysical methods to develop test procedures that can predict the characteristics of a hearing aid that are required for each individual to optimize his or her understanding of speech.

One team of investigators has standardized a procedure using auditory evoked potententials (ABR) and frequency-specific stimuli in order that a graphical representation of a young child's hearing can be obtained. They are now using it clinically to select hearing aids for young, pre-language infants.

Central Auditory System

Basic Studies

Spike-like signals received from the inner ear are further processed by the auditory nerve and the auditory brain stem until they reach the the auditory portion of the cerebral cortex. Currently, a method of studying the auditory network is to find a single nerve-unit whose activity can be recorded and present a variety of inputs to the ear and note the response of the unit for each type of input.

Anatomical studies are providing details of the organization of efferent innervation of the olivocochlear bundle in an effort to explain its functional role in the hearing process. Current findings indicate that there are dual and independent efferent innervations of the organ of Corti. In addition, information about the patterns of afferent input to the neurons of origin and of the patterns of synaptic distribution of these neurons to the cochlea are contributing to our understanding of the auditory process.

Causal and Predictive Factors in Disorders

Electrophysiological techniques are being used in the study of auditory nerve fibers, units of the brainstem and the auditory cortex. Components of the electroencephalogram that can be shown to be synchronized with sound stimuli are generally called auditory evoked responses (ABR). Such a technique is being employed with premature infants who present immaturity of many organ systems including the central nervous system. Furthermore, many such infants are exposed to ototoxic agents and are placed in high noise environments. The very high rate (about 10%) of peripheral auditory dysfunction defined for this population and the possibility of more precisely determining neurologic prognosis makes the ABR a valuable method for determining the integrity of the auditory system.

Another study of premature infants with and without intraventricular brain hemorrhages, identified high risk factors associated with prematurity. By measuring their auditory evoked responses, researchers are able to detect evidence of hearing dysfunction in these infants between 28 weeks and term and find it related to the occurrence of hyperbilirubinemia and hypoxia. Prevention of neurological sequelae in the preterm infant is the long range goal of this work which utilizes safe technology for early detection.

A study of right-left asymmetries in brain stem auditory evoked potentials on normal subjects showed that no significant asymmetries were found for most of the peaks including those representing auditory nerve activity. However, for the significant asymmetries identified in I(-), III(+) and IV(+), the larger peaks were associated with right ear stimulation. These same subjects showed some correlation between the evoked potential results and the dominant ear as demonstrated in a dichotic listening task.

Pharmacological studies intending to elucidate the cochlear mechanisms leading to auditory-nerve discharges indicate that most of the ototoxic effects of the diuretic drug, furosemide, appear to be on responses to low-level stimuli and can perhaps be related to changes in the endocochlear potential. Results of another experiment show clearly that the two major functions of the binaural

auditory system, localization (represented by interaural time discrimination) and signal selection (represented by masking level difference) do not function optimally when the auditory system is confronted by both tasks simultaneously.

Though cortical response to sound is poorly understood, it is assumed that higher-order processing of stimuli occurs in one or more of several areas of the auditory cortex. Studies underway show that auditory recognition and discrimination are related to task complexity, stimulus complexity and the interaction between the task and stimulus. So far, these relationships hold true for both normal listeners and those with hearing impairments.

Diagnosis, Treatment and Rehabilitation

Assessment of auditory dysfunction among patients with brainstem pathologies should eventually lead to the development of new diagnostic tests for diagnosing central auditory disorders and describing the auditory dysfunctions found in these patients. This is being pursued by comparing auditory brainstem responses and masking level differences in such patients to explain certain binaural phenomena.

Other studies are involved in the development of clinical tests of central auditory processing for use with patients who have concomitant peripheral losses. Binaural separation of sound stimuli is proving to be the most promising technique at the current time, but progress has been slow.

Biochemistry, Neurochemistry and Pharmacology of Hearing

Basic Studies

Biochemical, neurochemical and pharmacologic studies have provided new insights into how chemical events subserve the characteristic activity of the peripheral and central auditory system. It has been through advances in quantitative analytical approaches that the acquisition of knowledge in these most important areas has progressed. The primary objective has been to provide a solid research base to explain biochemical events involved in sensory and neural processes. The information to date however, has not derived from chemical analyses alone. Different levels of complexity in both structure and function have relied heavily on concomitant derived data from neurobiology, neuroanatomy and neurophysiology. As a result of this working relationship between closely-allied areas, concepts and information which were widely dispersed have been formulated into meaningful hypotheses.

The research to date can be segmented into that which is concerned with inner ear cochlear tissues, cochlear fluids and VIIIth nerve neurons, and the cochlear nucleus within the brainstem. Of interest are the mechanisms of ototoxic drugs and their possible interaction with physical and other chemical agents. Experimental preparations include chinchilla, guinea pig, mouse, rat, frog and goldfish.

Biochemical and related studies of putative neurotransmitters of hair cells are under investigation. The afferent transmitter substance and possible associated enzyme system is being examined through the use of a lateral line preparation. By isolation and analysis of the synaptic vesicle fraction, the investigator hopes to identify the presumed neurotransmitter. Another approach is to characterize primary amines in the perilymph that may be involved in afferent transduction. Sound-isolated and sound-exposed animals are used and resultant

data are analyzed using microfluorescence high performance liquid chromatography (HPLC). Changes in levels of aspartate, arginine, and alanine are monitored. A similar approach tests several antagonists to glutamate receptors.

A combined biochemical and histochemical technique is used to study cochlear homeostasis. Studies include specific activity and histochemical localization of adenylate cyclase during development of the inner ear of the normal mouse, and the influence of hormones and neuromodulators (e.g., B-adrenergic agonists and blockers, vasopressin, parathyroid hormone, Prostaglandin PGE) on enzyme activity. Cochlear microphonic, endocochlear potential and whole nerve action potential also are measured in response to the hormones and neuromodulators. The effects of noise as well as overstimulation on energy metabolism is determined by 2-deoxyglucose capture. The hypothesis tested is that the decrease in energy metabolism observed with overstimulation is caused by vasoconstriction.

Other studies include the quantitative, electrochemical, electrophysiologic, and histological analysis of the normal and experimentally altered inner ear. The experimental model involves arterial perfusion of the inner ear of the guinea pig with synthetic blood in order to control the biochemical environment. Specific aims include: (1) evaluation of metabolic substrates in the organ of Corti, stria vascularis, and Reissner's membrane; (2) evaluation of putative transmitters in the organ of Corti in chinchilla; (3) evaluation of amino-acid profile in perilymph, endolymph, CSF, and blood by HPLC; (4) study of the effect of toxic substances on cyclic-adenosine monophosphate; (5) evaluation of the effect of interruption of the efferent cochlear fibers upon enzymatic pathways of the organ of Corti; and (6) evaluation of metabolism in genetic deficient inner ear and Kanamycin treated animals (Waltzing guinea pig). These projects are important since they may ultimately open the way to new types of pharmacologic therapy of hearing disorders.

As a foundation for work in this area, another investigator conducts neuropharmacologic studies of synaptic transmitter substances in the cochlear nucleus (CN). Putative excitatory neurotransmitters, namely glutamate and aspartate, are iontophoretically applied to single neurons in various regions of the CN. Since microneurochemical studies indicate that L-glutamic acid and L-aspartic acid show regional distributions within the CN complex, the principal investigator contends that iontophoretic application of the excitatory transmitters will, therefore, have differential effects in different areas of the CN. Glutamate, aspartate, and cysteic acid are assessed in terms of relative effectiveness in altering spontaneous activity; area specific response patterns are generated. The heterocyclic glutamate analog, kainic acid and the aspartate analog, N-methyl D-aspartate, are examined for their effect. Specific antagonists are also investigated in this respect.

There is a further long-range effort to understand the synaptic chemistry of the cochlear nucleus of the auditory brainstem, by histochemical examination of cholinergic structures. The basic methods involve quantitative histochemistry. Four specific aims are listed based on monitoring the levels of cholinergic enzymes. First, the principal investigator proposes to determine the relative proportions of choline acetyltransferase and acetylcholinesterase activities in subregions of the rat cochlear nucleus that are related to centrifugal pathways; second, he will determine the origin and routes of the centrifugal pathways; third, he will

measure cholinergic enzymes in the olivo-cochlear bundle; and fourth, examine similar regions in the cat where the anatomy is more firmly established. These studies are designed to determine chemical efferent activity in the auditory brain stem similar to that which has been found anatomically and physiologically.

Diagnosis and Treatment

Once symptoms of drug ototoxicity are detected, it would be beneficial to be able to treat or alleviate the condition prior to permanent effects. A project related to this goal is designed to detect complexes formed during inactivation of gentamicin by carbenicillin, and to investigate its ototoxic effects in the guinea pig model. Studies focus on three areas: (1) identification and characterization of the gentamicin-carbenicillin reaction products (G-C), (2) pharmacokinetics of G-C in patients with various degrees of renal failure who are treated with gentamicin and carbenicillin, and (3) testing of G-C for ototoxic potential in an animal model (guinea pigs). The investigators isolate and characterize G-C complexes by silica gel thin-layer chromatography, electrophoresis, counting of radioactivity, differential binding to phosphocellulose, high-pressure liquid chromatography, and gel-filtration. The critical goals involve the demonstration in vivo of G-C complexes and subsequently, its ototoxicity. Baseline vestibulometric and cochleometric testing are utilized.

Another approach to the problem of ototoxic-induced hearing loss is to explain the molecular mechanism underlying the drug action. Cellular actions and the structure-toxicity relationships are explored. The hypothesis tested is that aminoglycosides interact with polyphosphoinositides in monomolecular films and liposomes. It is thought that the aminoglycosides act at the membrane level by lowering permeability barriers, and that this potentiates the effect to other ototoxic drugs. Certain drugs are tested for reversibility. Data to date support the hypothesis that a disturbance of polyphosphoinositide turnover is a contributing factor in ototoxicity.

Auditory Prosthesis Research

Basic Studies

Profoundly deaf subjects do not for the most part benefit from a conventional hearing aid. In order to overcome this problem, efforts have been made to utilize electrical auditory nerve stimulating prosthetic devices. The objective is to restore hearing for speech. Physiologic, psychophysical, and speech science research have revealed that intelligible speech can be encoded by a nerve stimulation device consisting of a series of independent stimulation channels. The requirement for several discrete channels is not impossible. For example, if six to eight or more sectors of the auditory nerve array can be discretely electrically stimulated, it is quite possible to encode speech in profoundly deaf subjects.

A number of investigators are addressing the fundamental problems involved in auditory prosthesis research. These investigations are proceeding with the objective of discovering effective methods for stimulation with a multichannel cochlear prosthesis. The research involves fabrication of implantable multi-electrode arrays, interfacing multi-electrode arrays with the auditory nerve,

tests of these arrays in animals, determination of interelectrode interactions, assessment of cochlear ganglion cell survival, improvement in dynamic range, development of a transcutaneous multi-electrode driving system, and design of a sound-processor which provides maximum speech discrimination. This latter development will ultimately lead to fabrication of a wearable sound-processor.

Diagnosis, Treatment and Rehabilitation

The task at hand is the development of multichannel sound processor-stimulator. Studies toward this goal include: (]) psychophysical investigations of the reactions of profoundly deaf patients to electrical stimulation, (2) spatio-temporal representation of speech elements, (3) special speech testing of implant patients, (4) definition of psychophysical and electrophysiologic patterns, (5) determination of the status of surviving auditory nerve elements, (6) stability of implant operation over long time periods, and (7) safety factors of implant devices. Specific consideration is given to problems inherent in application of implant devices in deaf children.

One investigator has fabricated two multichannel printed circuit teflon ribbons contained within a silicone rubber carrier. The aim is to produce a device which will be frequency specific, small and flexible and contain 30 conductors and electrodes necessary for]5 biplar channels.

A somewhat different approach is taken by another investigator towards the development of a multichannel cochlear prosthesis. This investigator is developing an eight-channel, polymide, flexible thin-film electrode. All electrodes undergo in vitro testing prior to implantation in cats, while additional ones will undergo saline testing for as long as two years. Once electrodes pass the in vitro testing period, cats will be implanted. Ultimately, profoundly bilateral deaf adults are to be implanted. A variety of electrophysiologic and morphological studies will be used to test for mechanical or electrical damage. This research proceeds from the notion that the modiolar electrode array is not adequate, and that a flexible scala typmpani electrode is the array of choice. A complete battery of otologic, neurologic and psychological tests will be administered. After implantation, extensive psychophysical, speech, electrophysiologic and other data will be collected to determine the efficacy of the multichannel electrode array. With these developments, the potential for continued progress of multichannel arrays is promising.

Equilibrium and Balance

Basic Studies

Progress has been made in understanding how the peripheral and central vestibular systems process information. This has occurred despite the complexity of the vestibular labyrinth, its afferent pathways, central mechanisms, inputs from the visual and proprioceptive systems, superimposition of various other sensory systems, and the convergence of disorders that affect the peripheral and central vestibular systems.

Contributions from the fields of neuroanatomy, neurophysiology, immunology, and biochemistry have served as a foundation for basic vestibular research studies, and the clinical disciplines of otology, neurology and audiology have derived

specific information being on disease etiology and pathogenesis. Clinical investigations on equilibrium and balance have translated fundamental knowledge to treatment and prevention regimens, which in turn may require major testing in clinical trials. It remains to be seen whether demonstration programs will test the feasibility of mounting prevention, treatment and education programs in specific settings on specific vestibular problems. Once a firm basis of knowledge has been established its application on the clinical level becomes possible.

The Institute has a major responsibility for vestibular disorders and diseases. The significance of this responsibility and the challenge it represents can only be appreciated when considered in light of the devastating effect that equilibrium and balance problems have on maintenance of posture, locomotion, social interaction and work environment. Specific research projects in this scientific area include morpho-physiologic studies of secondary vestibular neurons, studies of structure and function of afferent vestibular pathways and intracellular dye injections of vestibular axons so as to trace peripheral and central projections. To demonstrate vestibular efferent projections from individual christae and maculae of the semicircular canals, the HRP-TMB histochemical technique is used by another investigator. Transynaptic projections are studied using ^{3}H-labeled proline-fucose, and fluorescence techniques are used to investigate catecholaminergic neurons in reticular formation. Accurate two-plane (coronal, sagittal) neuronal maps are constructed so that further definition of morphology accrues, which will provide further guidance for electrophysiologic studies.

Processing of visual and vestibular signals to produce eye movements and body postural responses relates to the fundamental studies of anatomy and physiology discussed above. In this effort, a vestibular mechanism responsible for information storage of slow-phase eye velocity has been implicated. Investigations in this area are directed towards basic mechanisms responsible for producing vestibular nystagmus, optokinetic nystagmus (OKN) and visual vestibular interactions. It has been observed that stored neural activity promotes ocular-following during OKN and is responsible for optokinetic after-nystagmus, which lengthens the time over which compensatory eye movements are maintained. The decay-time constant of neurons in the vestibular nuclei are longer than those found in canal afferents. Manifestations of stored activity are found in neurons in the vestibular nuclei of monkey. Research indicates that such a velocity storage mechanism is present in man. While it may play less of a role in man, the mechanism has been found to be important in mediating visual-vestibular interactions.

The avian, amphibian and mouse embryo otocyst are being used as organ culture models in studies of synaptic specialization in vestibular sensory epithelia, vestibular innervation, and synaptic junction modulation of afferent and efferent projection systems. Light and ultrastructural level studies form the basis for analysis of successful explants. Freeze fracture analysis is used for the mature and developing intramembrane studies. The experimental preparations selected provide both phylogenetic comparisons and a common basis for correlation of the various experimental studies.

Using electrophysiologic techniques, investigators are examining postural reflexes in the neck and forelimbs which respond to otolith stimulation. Decerebrate and semicircular canal-plugged cats are tested on a computer-driven tilt table. Information is thus derived about the sensitivity of various muscle groups to

tilt, sensitivity of vestibular neurons to tilt, and identification of the afferent projection of vestibular neurons. Tonic and phasic neurons are investigated. The function of the medial and lateral vestibular spiral tracts also are tested.

In other studies of the vestibular system, information is derived concerning the mechanical aspects of selective filtering and transduction, and the effects of peripheral signal integration in the inner ear. The aim is to deduce the physical bases of various sensory properties of the inner ear. The experimental animals are the American bullfrog and gerbil. Measurements are made of the resting potential and response properties of single afferent fibers in the inner ear which are sensitive to gravitational stimulation. Once the physiological properties of fibers have been characterized, they are dye marked by iontophoretic injection of lucifer yellow. The specimens are then examined by fluorescence microscopy in order to determine: (1) fiber diameter, organ of origin in inner ear, number of cells innervated by fibers and their location within sensory organs and, in some cases, central termination of fibers; (2) examination of tectoria, cupulae and otoconial membranes in frozen, freeze-fractured specimens and freeze-dried specimens. Because the vestibular nuclei have not been well characterized in the bullfrog, Golgi impregnation and other standard neurohistologic methods are used.

Diagnosis, Treatment and Rehabilitation

A system is under development to measure vestibular control of posture with a view toward clinical testing of otological and neurological patients. The major goal of this research is to determine whether a test that measures the patient's postural system, or the ability to maintain posture, can detect a vestibular lesion. Patients are placed on a platform which, by making changes in ankle angle, stabilizes the ankle joint during rotation. Vision is eliminated by eye closure. Motion is measured by video camera pictures of lights applied at various points on the body surface. This study also examines a patient's ability to adapt to perturbations in visual or somatosensory inputs. These perturbations are brought about by varying the visual field motion relative to the patient's head or by applying linear translation to the supporting surface. The objective is to delineate the normal and abnormal responses to this test.

Refinement of posturographic techniques used in clinical evaluation of patients with disorders of balance continue. Data have been obtained with patients and normal subjects. These quantitative studies of human posture control mechanisms use the simultaneous center of force and head trajectory recordings. Controlled visual and galvanic vestibular inputs to vestibulo-spinal control system are employed in order to characterize time and frequency domain human postural control responses and to study visual-vestibular interactions. The transfer characteristics between the human head and center of mass movements are determined. In addition to force platform recordings, EMG responses for muscles controlling ankle-joint positions are obtained for comparison with force platform analysis of posture control. Selected patient groups with converging neural musculo-skeletal system abnormalities are studied as abnormal control groups. Mathematical models of the multi-linked human postural control systems are employed to optimize the postural reflex control mechanisms in normal and vestibular deficient humans.

A microprocessor-based system for vestibular function testing is under development and a clinical trial is being prepared. A library of nystagmus records will be developed and nystagmus tests will be standardized. If realized, an automated system could become available to clinicians to standardize vestibular tests. The specific instrumentation used are a microprocessor-based instrument which collects and analyzes nystagmus recorded via electrooculography, a rotating chair and accompanying optokinetic device, and caloric stimulators which are controlled by the microprocessor. Prototypes for all devices have been assembled and partially tested. Continued development of a data base of human evaluations of eye movement data which can be compared with the computer evaluations are planned. The goal is to define a quantitative method by which the device algorithm for nystagmus analysis can be made to match human performance in the reading of nystagmus records. Further aims are to improve the real-time nystagmus program for artifact rejection and the detection of fast phase and eye blinks, and to evaluate the device in a clinical setting. Completion of these objectives will accomplish a specific practical goal for intervention research.

The vestibulo-toxic effects of aminoglycoside antibiotics on the dynamics of the human vestibulo-ocular and vestibulo-spinal reflex systems are being studied, as are the adaptive properties of these reflexes following total loss of vestibular function. Patients receiving aminoglycoside antibiotics are tested with various combinations of oculo-motor pursuit, optokinetic and rotational vestibular stimuli. Upright postural control is studied by manipulation of visual and ankle joint proprioception in patients with aminoglycoside induced vestibular ototoxicity. The results should significantly advance the health care of patients receiving ototoxic antibiotics by providing sensitive quantitative methods for early detection of vestibular aminoglycoside ototoxicity, provide vestibular incidence figures for several commonly used aminoglycoside antibiotics, and provide information about adaptive motor reflex mechanisms. These data will be of value in designing more effective rehabilitative treatment protocols.

Disorders of the Ears, Nose and Throat

Basic Studies

Basic studies on etiology and pathogenesis have received major attention. Studies continue in neuro-otology, anatomy, physiology and pathophysiology of the ear, middle ear response to otitis media, histopathology of animal and human temporal bones, ototoxic drug interactions, and laryngeal, pharyngeal and acoustical factors related to speech. This research has resulted in several discoveries, theories, and significant concepts which, in turn, have served as a basis for further research, refinement, development, evaluation and dissemination of research findings to several relevant disciplines such as otolaryngology, speech pathology, audiology, neurology, pediatrics and rehabilitative medicine.

Causal and Predictive Factors in Disorders

Despite the encouraging progress made by various investigators who are conducting basic research into the biologic process prior to the onset of an ear, nose or throat disease, much remains to be accomplished. As a result, research continues into basic mechanisms underlying diseases and disorders which manifest themselves in the outer, middle and inner ears.

Related to the outer and middle ears is an investigation on spontaneous and experimentally-induced aural cholesteatoma in an animal model--Mongolian gerbil. Anatomic, electrophysiologic and behavioral studies are conducted so as to shed light on the invasive and erosive characteristics of human aural cholesteatoma. So as to determine the natural history of this ear disease, the investigator employs auditory brain stem evoked responses (BSER), transmission electron-microscopy and cytocochleography. Of interest is whether spontaneous cholesteatomas are similar to those that are surgically-induced (via ear canal ligation). The investigator employs a procedure of surgically-imposing semi-permeable and impermeable barriers between the advancing front of the cholesteatoma and the base of the middle ear. Since erosion of the middle ear bone usually takes place as a result of the advancing mass, he will determine whether bone erosion is due to pressure, enzymatic protease action, cellular osteoclast action, or a combination of these factors. A related but different study is investigating cholesteatomas as a result of skin and inflammatory granulomas in the guinea pig middle ear. Morphologic and immunocytochemical studies at the light and ultrastructural level are used to localize and quantify a specific collagenolytic enzyme.

Attention continues to be devoted to the most common middle ear problem in children --serous otitis media with effusion. Several investigators are examing the immune response of the middle ear, mucociliary fluid clearance, microbiologic factors, underlying pathogenesis, concomitant mechanical properties, and 3-D reconstructions of the tympanic membrane in normal and diseased ears.

Immunologic aspects of the middle ear are of major importance. Whether the bacteriostatic substances in an effusion develop tolerance for the disease, whether the initial ear infection prevents the development of an adequate immune system, or whether further infection is caused by the immune response are questions that may be answered using immunologic methods.

A model of the immune response in the middle ear of the guinea pig has been developed utilizing keyhold limpet hemocyanin (KLH). Various related topics under investigation include immune as opposed to systemic responses, immune expression, identification of B- and T-cell lymphocytes, identification of specific antibody-producing cells, and characterization of the role of immunoglobulins and immune lymphocytes. The human disease is further characterized as to cellular and humoral response, variation in sensitization-challenge intervals, development of chronic effusion, and contribution of the local immune response to chronic effusion and inflammation. The pathophysiologic consequences of the middle ear response are also being examined, together with regulation of the response by both immune and pharmacologic inhibitors.

Related to this problem is whether muco-exudates produced by otitis media may accumulate instead of clearing through the Eustachian tube. Previous findings have firmly established that middle ear fluid must have the character of an incipient gel if proper clearance by ciliary action is to take place. Not being normally a permanently cross-linked system, mucus undergoes spontaneous structural changes. Hence, the effectiveness of clearance can be linked to the number of cells producing mucus, the amount produced, the rheological character of the secretion and the nature of the muco-ciliary wave interaction. The glycoprotein macromolecular aggregates from which mucus derives its special rheological properties are probed. The studies continue to be directed towards the structure of the glycoprotein entity, the distribution of cross-links, the mechanics of ciliary beat and the factors controlling mucus production.

In summation, major investigations on various forms of otitis media include the basic disciplines of anatomy, physiology, biochemistry, immunology, and bacteriology. The role of the infectious process, Eustachian tube dysfunction, the immune response, and the sequelae of otitis media (granulation tissue, cholesteatoma, cholesterol granuloma, subsequent sensorineural hearing loss, etc.) are receiving concerted and coordinated attention.

While significant progress has been made on diagnosis, identification of causal factors and treatment of outer and middle ear disorders, the same cannot be said of the inner ear. Further work is needed in preventing inner ear diseases.

Morphological studies using both transmission and scanning electron-microscopy are used to provide detailed accounts of the inner ear of animals. A major goal of this research is to correlate animal findings with normal human temporal bones. Special emphasis is placed on the structure of the spiral ganglion cells, nerve fibers in the osseous spiral lamina, as well as their distribution in the organ of Corti. The concept that morphological changes of the endolymphatic sac and ductus reuniens may play a role in controlling endolymphatic hydrops is examined. Transport of horseradish perosidase (HRP) into frog auditory neurons using sophisticated chromagen techniques such as tetramethyl benzidene (TMB) continues to be explored. Studies of the acoustic reflex-cochlear route, the human auditory nerve potential, and the BSER continue to receive considerable attention as diagnostic tools for both children and adults.

Research into basic fundamental mechanisms of the vestibular apparatus continues. Development and refinement of techniques to evaluate functional alterations after partial ablation of the vestibular system and the system's subsequent compensation are proceeding. Work at the light and electron microscopic level on the human saccule and utricle, otoconial membranes, and other vestibular portions of the ear have added new insights into this difficult area. Progress has been made in the study of proprioceptive and visual input enhancement of vestibular system-induced imbalance. Recently, ultrastructural alterations in the vestibular ganglion after labyrinthectomy have been confirmed. These findings are related to the study of ultrastructure of commissural fibers of the vestibular nuclei in the squirrel monkey. These studies are likely to become standard reference data for other investigators in this and other closely-related areas.

Of interest in the area of laryngeal dysfunction is the brain stem control of laryngeal muscles. Using a stimulating and recording method for intact laryngeal motoneurons, investigators have characterized individual motor units in anesthetized non-human primates. The thrust of the research is to determine function, recruitment sequence, axon conduction velocities and muscle fiber contractile properties. The histochemical method is used to characterized the muscle fiber motor unit. Germane to these studies is to ascertain location and cell body morphology in the brain stem using HRP tehniques. A final set of experiments characterize these same motor units during vocalization.

On a more molecular level, biochemical characteristics of various muscle fiber types are determined using quantitative histochemical reaction products. The aim is to quantify different enzymes and substrates that may indicate relative oxidative and glycolytic capacities of muscle fibers. Quantitative morphological parameters are obtained using serial sections processed for electron microscopy. Morphometric data include determination of Z-line width, volume densities of sub-sarcolemmal

mitochondria, myofibrils and intercellular lipid. Correlational studies of biochemical events and morphological architecture of intrinsic laryngeal muscle will assist in relating these findings to laryngeal function. Basic studies such as these should assist in providing a foundation for a better understanding of peripheral action, central control and biochemical events underlying laryngeal muscle contractions during human sound production.

The mechanism of action of ototoxic agents, singly and in such therapeutic combinations as aminoglycoside antibiotics (eg. kanamycin) with loop diuretics (eg. ethacrynic acid, furosemide) are being studied. In order to examine drug interaction experimentally, an animal model was developed and is used to determine time-dose-effect relationships. Ultrastructural sites within the cochlea at which the earliest damage occurs have been identified. Furthermore, non-aminoglycoside drugs have been found to have interactional effects. Sophisticated histochemical and autoradiographic methods are used. Thus, work continues on producing time-dose-effect relationships of several non-aminoglycosidic drugs found to interact at a level which causes lesions of the cochlea and vestibular mechanisms. The developing chick embryo model that is used to study ototoxic agents and their interactions, using electron microscopic techniques, has resulted in important new leads.

Diagnosis, Treatment and Rehabilitation

The clinical phase of the natural history of diseases or disorders of the ear, nose and throat also receives attention. Several of the studies noted above about the natural course of otitis media, cholesteatoma and other outer and middle ear disorders are directed toward alleviating the disability (and subsequent morbidity if untreated), after these conditions have been detected.

Information is being sought concerning the pathogenesis and possible treatment for idiopathic sudden hearing loss. Patients admitted into the study withing 10 days of their hearing loss undergo a complete otologic examination, audiometric studies, physical examination and evaluation for known causes of sudden hearing loss. Blood and serum are analyzed for viral antibody, cell-mediated immunity, and quantification of IgE, IgM and IgG. While spontaneous recovery often occurs following sudden hearing loss, a slight beneficial effect to steroid treatment has been documented. The determination of the relationship between virally-induced sudden hearing loss to other pathologic, demographic, or environmental factors are included. These studies should increase our understanding of the etiology, classification, and treatment of sensorineural hearing loss of sudden onset.

In a number of studies human temporal bone pathology is being examined and correlated with known audiologic, otologic, behavioral and physical findings. One study places special emphasis on Meniere's disease and other types of endolymphatic hydrops. Other studies are less narrowly focussed, temporal bones from a wider variety of clinical conditions being examined histologically and the findings related to clinical data. At times, bones are obtained in which ear disease may not be the primary concern; nevertheless, the cause of death and resultant histopathologic changes (e.g., leukemia) are of importance to otopathology.

Studies are being conducted on the symptomatology, etiology, cause and typology of spastic dysphonia. The long-term goal is to evaluate the effectiveness of surgical treatment by unilateral recurrent laryngeal nerve section, evaluate secondary procedures for recurring spasticity, identify causative mechanisms of spastic dysphonia, establish criteria for vocal tremor, and determine the microanatomy of the recurrent laryngeal nerve. Acoustic, aerodynamic, glottographic, psychophysiologic, electromyographic and pharmacologic studies are conducted. The combined efforts of researchers in speech and hearing sciences, otolaryngology, neurology, physiology and pathology are utilized.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

UNIVERSITY OF FLORIDA (NO1-NS-5-2313)

Title: Auditory Sensitivity in Young Children

Contractor's Project Director: Donald C. Teas, Ph.D.

Date Contract Initiated: June 30, 1975

Current Level of Support: $0

Objectives: This contract was awarded to study auditory sensitivity in young children. The goal was to develop and evaluate a battery of tests which could be used to characterize the hearing sensitivity of young chidren not suspected of having hearing deficits and to examine the feasibility of using such a battery to assess the hearing of infants and young children who are suspected of/or at-risk for hearing dysfunction. Particular emphasis was placed on the developmental aspects of the hearing ability of this population.

Methods Employed: Auditory brain stem responses (ABR) were obtained for infants to broadband clicks with center frequencies of 500, 1,000, 2,000, 4,000 and 8,000 Hz and intensities of 20, 40 and 60 dB (above normal adult threshold). Blink inhibition by acoustic leadtone measures were developed for use with patients aged 2 to 30 months. A visual reinforcement paradigm with children under 3 years employed test frequencies of 500, 2,000 and 8,000 Hz.

Major Findings:

1. The ABR work showed that the 8,000 Hz filtered click was the most effective stimulus for eliciting Waves I, III and V and the 1,000 Hz stimulus was the poorest. Wave V was the most sensitive measure for all stimuli. A clinically usable test should include stimuli at both 2,000 and 8,000 Hz.

2. Ninety percent of the infants showed significant blink inhibition by 25 msec for tones presented at 40 dB SPL.

3. Infants from 6 to 18 months of age showed thresholds within 15 dB of adult norms for all frequencies tested. Six-month-olds were significantly less sensitive to 8,000 Hz than to either of the lower frequency stimuli, but older infants demonstrated approximately equal sensitivity for all frequencies tested.

Significance to Biomedical Research and the Program of the Institute: Procedures were needed to assess hearing of young children who are incapable of providing conventional responses. A battery of tests to determine hearing sensitivity at different developmental stages is essential to the initiation of a habilitation program to optimize language and psychosocial development.

Proposed Course: Contract was completed on December 30, 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

MINNEAPOLIS MEDICAL RESEARCH FOUNDATION, MINNEAPOLIS, MINNESOTA (N01-NS-7-2378)

Title: A Comprehensive Study of the Language Recovery Process in Adults with Aphasia Following a Cerebrovascular Accident

Contractor's Project Director: Alan B. Ruben, M.D.

Date Contract Initiated: September 30, 1977

Current Annual Level of Support: $315,155

Objectives: The purpose of the research is to develop increased understanding of the neurophysiological and behavioral bases of the language recovery process in aphasic adults. Multidisciplinary studies will determine:

1. The relationship between outcome of aphasia and the size and location of brain pathology and neurophysiological activity in each hemisphere.

2. The relationship between changes in neurophysiological activity of either hemisphere, and degree of language recovery.

3. Whether cognition is associated with the degree of recovery from aphasia.

4. Whether verbal learning/memory deficits are associated with degree of recovery from aphasia.

Methods Employed: Aphasia patients are examined monthly between one and six months following the onset of aphasia due to a cerebrovascular accident. Metabolic patterns during language and non-verbal behavior in each hemisphere are being examined with xenon inhalation cerebral blood flow and spectral analysis of EEG recordings. CT scanning is carried out on admission to the research and at one month post onset; speech and language, dichotic listening, verbal learning and memory and cognitive testing are carried out at regular intervals over the first six months.

Major Findings: Analysis of the first 24 cases on the cerebral blood flow data indicate: no consistent changes in right hemisphere flow between 2, 6 and 12 months post onset and no relationship between right hemisphere flow or change in flow and language recovery. In patients with good auditory comprehension, the flow was greater in the left temporal probes than in the patients with poor auditory comprehension. No changes were found in the degree of alpha suppression in either the left or right hemispheres which could be associated with language recovery. Thus far, these metabolic studies do not provide support for the theory of increased involvement of the right hemisphere in language functioning during recovery from aphasia.

Studies of verbal learning in aphasia indicate patients are able to acquire new information and store it; however, those with frontal opercular lesions have greater difficulties with list learning. Memory span, on the other hand, is impaired independently from list learning and language recovery, and may not be as important in aphasia recovery as list learning performance.

Significance to Biomedical Research and the Program of the Institute: Language recovery in aphasic adults is not well understood. In most cases recovery is rapid during the first nine weeks following the onset of symptoms. The size and location of brain lesions, regional blood flow, and physiological response of each hemisphere during verbal behavior will determine the association between dominant hemisphere status and level of recovery from aphasia. If recovery is not highly associated with changes in the left hemisphere, and the right hemisphere is found to be involved in verbal functioning, both the right and left hemispheres may be involved in language recovery following a CVA. The results will be useful for developing appropriate approaches for treatment.

Proposed Course: The contract was extended for one additional year to complete testing of close to 55 subjects. Termination date is March 31, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

UNIVERSITY OF ILLINOIS (NO1-NS-7-2380)

Title: Evaluation of a Test of Speech Perception in Noise

Contractor's Project Director: Robert C. Bilger, Ph.D.

Date Contract Initiated: September 29, 1977

Current Annual Level of Support: $0

Objectives: The purpose of this contract was to conduct experimental work to determine the interlist equivalency, performance by signal-to-babble (S/B) functions and validity of the Speech Perception in Noise (SPIN) Test.

Methods Employed: Interlist equivalence of all ten recorded forms of the SPIN Test were determined on a sample of 128 hearing-impaired adults by generating alpha coefficients, intercorrelations between all ten forms, variance estimates for error and obtained variances for each form, and mean performance. Lack of equivalence among forms required item analyses and generation of eight new forms that met the equivalence criteria. All forms were administered to subjects with other speech stimuli to determine the degree to which the SPIN Test over- or under-estimates speech perception in noise compared to other measures of speech recognition. The validity of the SPIN Test was determined with 40 additional hearing-impaired subjects who were fitted with hearing aids. A paradigm was followed to obtain validating data with a test of the relative effectiveness of the subjects' communication via visual, auditory and combined cues when wearing a hearing aid; a set of psychological tests selected to measure his cognitive adaptability; tests of linguistic competency; and, a test of Communication Ability in Daily Living. Three to four months later, the subjects were reevaluated on several measures of communication effectiveness to assess the efficacy of the hearing aid.

Major Findings:

1. The non-auditory test developed to assess the ability of these hearing-impaired people indicates the semantic and redundant cues employed by them to ascertain the final words in highly predictable sentences.

2. The eight revised forms of the SPIN Test are equivalent and can be used interchangeably and repeatedly.

3. SPIN Test results correlate well with other selected measures of speech recognition. Clinical applicability of the SPIN Test is undergoing further evaluation.

Significance to Biomedical Research and the Program of the Institute: Assessment of supra-threshold speech perception in noise will provide a valuable tool for the practicing clinician in managing hearing-impaired patients. There is a high probability that the SPIN Test will have predictive value in determining the degree of benefit that persons with acquired sensorineural hearing impairments may appreciate from a properly selected hearing aid.

Proposed Course: Final data analyses and reports are being prepared. Contract completion date was August 31, 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

CHILDREN'S HOSPITAL OF PITTSBURGH (NO1-NS-8-2384)

Title: Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME)

Contractor's Project Director: Charles D. Bluestone, M.D.

Date Contract Initiated: July 1, 1978

Current Level of Support: $0

Objectives: To determine if a combination of an oral decongestant and antihistamine medication (D & A) is effective in the treatment of otitis media with effusion.

Major Findings: A total of 611 subjects from 7 months to 12 years of age were enrolled during the period from July, 1978 - June, 1981. Over 90% (N=553) returned for the four-week examination. The outcome of the trial was based primarily on the presence or absence of OME. Of the 278 (50.3%) subjects with either unilateral or bilateral OME at entry into the program who received D & A, 69 (24.8%) had no effusion in either ear at the four-week endpoint. A similar figure was found for the children who received a placebo (N=67 of 275 subjects, or 24.3%). Within the D & A group and within the placebo group who entered with bilateral OME, both groups exhibited unilateral (or bilateral) OME at the four-week endpoint. No significant differences were found for either group as a function of age or duration of OME. Other possible related factors as to outcome were analyzed, such as sex, race, bilateral vs unilateral OME, previous history of OME, presence or absence of upper respiratory allergy, upper respiratory tract infection, rhinorrhea, adenoid size, season and socio-economic status. No significant differences were found between the two groups for any of these stratified factors. Some side-effects were noticed for the D & A group. Subsequent development of acute suppurative OME or purulent rhinitis was similar for both groups. Drug compliance, recurrence rates and hearing status were similar for both the experimental and control groups.

Significance to Biomedical Research and the Program of the Institute: A combination of oral D & A failed to reveal any beneficial effect in eliminating OME after four weeks of treatment; therefore, D & A is not an effective treatment for OME in infants and young children.

Proposed Course: The contract terminated on June 30, 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

PRESIDENT AND FELLOWS OF HARVARD COLLEGE, CAMBRIDGE, MASSACHUSETTS (N01-NS-8-2399)

Title: Laryngeal Carcinoma: Identification of High Risk Factors

Contractor's Project Director: Kenneth J. Rothman, M.D., Ph.D.

Date Contract Initiated: September 29, 1978

Current Annual Level of Support: $0

Objectives: To identify individual health, environmental, and occupational factors which will delineate persons at high risk of laryngeal carcinoma in the United States today. The following objectives will be met:

1. An integration of data available on factors associated with a high risk of laryngeal carcinoma in the United States;

2. An examination of mortality, incidence data and time trends to identify regions with significantly high rates of laryngeal cancer over the last 10 years; and,

3. Investigations of occupational factors and their relationship with laryngeal carcinoma.

Methods Employed: Data from the Commission of Professional and Hospital Activities, an organization which gathers information on about 40 per cent of the country's hospital discharges, were analyzed to determine regional differences in the incidence of laryngeal carcinoma. Time trends were examined across 1970 -1978 by region and sex. Data from the Third National Cancer Survey (TNCS) were evaluated to determine the interaction between alcohol and tobacco in laryngeal cancer. Interview data from the TNCS were also examined to determine which occupations had rate ratios greater than one.

Case control studies were conducted in Augusta, Georgia and New Haven, Connecticut to examine the risk ratios of different occupations for laryngeal carcinoma.

Major Findings: In the case control study conducted in Augusta, Georgia, rate-ratio estimates were greater than one for the following occupations: workers who separated filtered or dried textile fibers (RR=2.6); grain farmers (corn and soybeans) (RR=4.9); laborers and maintenance personnel (RR=5.4); mechanics (engine, electric motor, miscellaneous mechanics, millwrights, and repairmen (RR=1.4) and truck drivers, taxi drivers and chauffeurs, bus drivers and deliverymen (RR=1.1).

Significance to Biomedical Research and the Program of the Institute: The chances of survival following laryngeal carcinoma can be significantly enhanced with early treatment and the vocal mechanism may be spared when surgical intervention is not necessary. Screening programs are needed of persons at high risk of laryngeal cancer (such as industrial male workers who are heavy

smokers and drinkers between 60 and 65 years of age). Before such programs can be initiated, a clearer understanding is needed of what factors could delineate persons at high risk for this disease. The final report of this project will indicate what further research is needed for delineating persons who are at high risk as well as what is currently known about the relative risk for this disease in various sections of the population.

Proposed Course: Both Phase II and III of the research have been completed by the contractor; a case control study of the relationship between occupational histories and the occurrence of laryngeal carcinoma will be completed by June, 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA (N01-NS-9-2305)

Title: The Acquisition of Language and Communicative Skills by Speech and Sign in Infantile Autism

Contractor's Project Director: Thomas Layton, Ph.D.

Date Contract Initiated: March 31, 1979

Current Annual Level of Support: $51,092

Objectives: To conduct an experimental study of the development of communicative skills by autistic children when training involves only speech stimuli, only sign stimuli, speech and sign stimuli presented simultaneously, or speech and sign presented independently. The research will determine after six months of training which method of language training results in greater expressive and receptive language skills; greater use of language skills for communication; and greater retention of language skills following training. The study will also determine whether autistic children evidence cross-modality transfer of information learned in speech or sign to the other modality; whether simultaneous presentation of stimuli in two different modalities interferes with learning; and whether autistic children show similiar language learning difficulties in both the speech and sign modalities.

Methods Employed:Children with infantile autism are randomly assigned to different language training methods: with speech alone, with sign alone, with alternating instruction between speech and sign and with speech and sign combined.

Major Findings: A total of 36 children have completed the training program with six more included and nearly finished. The results of initial language development testing on admission to the study, are related to performance in language training. Children whose expressive language is initially superior to their receptive language, are most difficult to predict in their language training results while two other groups are more predictable. The group with relatively good overall performance on expressive and receptive testing and better performance in receptive items demonstrated a more rapid learning rate than those with generally poor performance on all language testing and only slightly better receptive language.

Significance to Biomedical Research and the Program of the Institutes: Impaired speech and language development is common to all children with infantile autism although the degree of impairment varies among children. The etiology of these disorders is not known and the bases for these children's specific difficulties in learning language is not well understood. Some have proposed auditory and speech processing difficulties which could account for these impairments. Recently, there have been clinical reports of marked success with some of these children in learning language using signs or gestures. Further reports indicate that once such children begin to use signs to communicate they may vocalize spontaneously and develop speech for

communication more readily. This research will examine these issues experimentally and have significance for the development of improved speech and language training for autistic children.

Proposed Course: The final phase is being extended without additional funds to allow time for report writing to March 31, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

UNIVERSITY OF CALIFORNIA, SAN DIEGO (N01-NS-9-2322)

Title: Evaluation of the Outcome of Preschool Impairment in Language Development

Contractor's Project Director: Paula Tallal, Ph.D.

Date Contract Initiated: September 30, 1979

Current Annual Level of Support: $64,200 (forward funded, annual support approximately $260,000)

Objectives: To determine, through a longitudinal intensive study, the outcome of preschool impairments in language development. In particular, the research will determine:

1. Whether the patterns of development of language, speech, listening and learning skills found in four-year-old, language-impaired children differ from those of normal children when both groups are examined annually between four and nine years of age.

2. Whether preschool children impaired in language development have greater difficulties in acquiring reading and writing skills than normal children at six, seven, eight and nine years of age.

3. Whether preschool children impaired in language development are impaired in their verbal learning, memory and scholastic achievement in comparison with normal children at five, six, seven, eight and nine years of age.

4. Whether certain familial and language, speech, listening and learning characteristics of language-impaired children at four years of age, are predictive of their language, reading, writing and scholastic abilities at five, six, seven, eight and nine years of age.

Methods Employed: One hundred language-impaired children are being examined annually between four to nine years of age with multidisciplinary investigations into their patterns of development of language, learning and memory, cognition, reading and writing. Two control groups, one chronologically similar and the other at an equivalent mental age, are also being followed for comparison of their developmental patterns with those of the experimental group.

Major Findings: The contractor is close to completing the selection and first year of testing of the language-impaired subjects for the investigation. Subject acquisition has been difficult since many subjects referred as language-impaired do not meet the rigorous subject selection criteria.

Subsequent to completion of the pilot testing, the testing battery was reduced to include items sensitive to age and which differentiate between normal and language-impaired subjects. A new language assessment battery was developed for this project which is far superior to any currently available and will be a significant new tool for the assessment and study of language-impaired children. The research will examine the validity of the assessment battery for assessing language development in language-impaired children and for discriminating normal and language-impaired children at each age level.

Significance to Biomedical Research and the Program of the Institutes: The research will provide critically needed information for treatment of children's language disorders. It will determine whether language-impaired children differ from normal in their language acquisition process or are simply delayed in the normal sequence of language acquisition. Until information is obtained on the language development process in language-impaired children, appropriate treatment approaches cannot be developed.

The research will also determine whether preschool impairments in language development are precursors of difficulties in learning to read and write. The research will provide a detailed analysis of the types of difficulties these children have when learning to read. With improved understanding of the reading deficits of children who have a linguistic difficulty, remedial procedures for this segment of the reading-disabled population can be improved.

Proposed Course: A contract was awarded for the first three years to include the developmental phase, subject selection and the first eighteen months of the longitudinal study. A Technical Merit Review site visit will be held in September 1982 before extending the contract for the final four years of the study.

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER (NO1-NS-0-2328)

Title: Efficacy of Adenoidectomy/Tympanostomy Tubes for Persistent Otitis Media with Effusion (POME)

Contractor's Project Director: George A. Gates, M.D.

Date Contract Initiated: January 1, 1980

Current Level of Support: $424,447

Objectives: To conduct a controlled clinical trial to determine the efficacy of various treatment modes for persistent otitis media with effusion (POME). The treatment consists of myringotomy (MX) without or MX with tympanostomy tubes (MXTT), adenoidectomy (AD) and a combination of all three treatment modes (MXADTT). The primary aim is to determine the most effective treatment for improved hearing and prevention of recurrent middle ear effusions.

Major Findings: A total of 1,080 screening evaluations have been completed (12/31/81). This number represents 81% of a predicted load of 1,340 for this time period. The attrition rate, however, has been higher than expected. Approximately 40% of the children have been disqualified prior to randomization. Approximately 30% of the remaining children were cleared medically and, therefore, were not randomized. Thus, a total of 124 patients (24%) have been randomized. Preliminary analyses of these data indicate that MXTT and MXADTT offer the best treatment for POME. Questions which have not been answered are the extent to which surgical retreatment might occur for each treatment group, surgical complications (e.g., drainage, cholesteatomas) experienced for the MXTT and MXADTT groups, number of treatment failures, and number of months with consecutive or intermittent effusion.

Significance to Biomedical Research and the Program of the Institute: Otitis media with effusion (OME) is one of the major health problems in children. Currently, there is no consensus as to the most efficacious treatment of this vexing problem using the four treatment modes. Preliminary information points to the effectiveness of two of the four treatment procedures.

Proposed Course: This contract is due to terminate on January 31, 1985. Due to the longitudinal nature of the study, and the problem of accumulating a sufficient number of patients to be randomized, the study should continue for the full five-year period.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

PURDUE RESEARCH FOUNDATION (NO1-NS-0-2329)

Title: Determination of Effects of Hearing Aid Amplification on Children

Contractor's Project Director: Carl A. Binnie, Ph.D.

Date Contract Initiated: March 31, 1980

Current Annual Level of Support: $109,287

Objectives: The purpose of this contract is to determine the possible effects of hearing aid amplification on the residual hearing of children with sensorineural hearing loss. It will relate hearing changes to the electroacoustic characteristics of the hearing aids, amount of hearing aid use, degree of hearing impairment, earmold or coupling system, etiological information and amount of progressive hearing deterioration.

Methods Employed: Baseline audiometric and tympanometric measures have been made. Changes in threshold are measured at predetermined intervals along with dosimetry and recordings of environmental noise exposure. Complete medical genetic evaluations are obtained as necessary. Function-gain measures are made in the soundfield for both aided and unaided conditions using computer-generated narrow bands of noise centered at the octave frequencies from 250-4,000 Hz.

Major Findings: Preliminary results indicate that hearing aid amplification has not significantly changed the hearing capabilities of any of the youngsters under study.

Significance to Biomedical Research and the Program of the Institute: The possibility of acoustic trauma produced by prolonged use of a powerful hearing aid has serious implications for the moderate to severely impaired listener. If such deterioration does occur, it will be essential for clinicians to take steps which will protect the inner ear from further damage and still provide the benefit of hearing aid amplification.

Proposed Course: Data will continue to be collected. Expected completion date is March 30, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

SYRACUSE UNIVERSITY, SYRACUSE, NEW YORK (N01-NS-0-2331)

Title: Methods for Studying Phonatory and Articulatory Control in Young Children Who Stutter

Contractor's Project Director: Edward Conture, Ph.D.

Date Contract Initiated: July 31, 1980

Current Annual Level of Support: $260,867

Objectives:

1. To develop measurement techniques and testing procedures for assessing the speech production skills of young children between four and six years of age which are noninvasive, objective and reliable.

2. To determine which aspects of phonatory and articulatory control during speech production differ in fluent and stuttering children between four and six years of age.

Methods Employed: The following procedures are being adapted for use with young children:

1. Surface electromyography is used to record from the orbicularis oris inferior (OOI) and the depressor labii inferior.

2. Voice onset time is measured from the electroglottograph and the sound spectrograph.

3. Vocal fold adduction is being measured from the glottal duty cycle of the electroglottograph.

4. Chest and abdominal components of respiratory movements are being measured from the Respitrace system.

5. Lower lip and jaw movements are being measured from strain gauges.

Speech is being sampled during rapid repetition of syllables, words and phrases and all signals are recorded simultaneously and digitized with time coding to allow for cross-correlations between different measures aligned for time.

Major Findings: In initial pilot studies, fluent utterances in normal speaking children and young stutterers were compared. The initiation of electromyographic activity in the OOI and the duration of OOI contraction synchronous with voice onset during syllable productions indicate that muscle contractions for labial closing gestures are synchronous with phonatory onset

in stuttering children during fluent speech rather than preceding phonation as occurred in the normally speaking children. Further, the stuttering children have shorter durations of OOI muscle contractions overall. These pilot data suggest that the bilabial contact gestures are too short in the fluent gestures of stuttering children and provide evidence that the temporal organization for speech differs from normal in stuttering children in other articulators besides the larynx.

Significance to Biomedical Research and the Program of the Institute: There is a critical need to stimulate research on stuttering; NINCDS is the prime BID within the U.S. Government for the support of stuttering research and only supports one grant in this area. Recent research on adults has indicated some differences in phonatory control between normal and stuttering adults. This project will examine the hypothesis of whether or not children who become persistent stutterers show differences in phonatory control during the normal developmental period of non-fluency.

Objective methods of assessing speech-timing control in young children who stutter will provide the necessary tools for research on the developmental period of non-fluency and the development of stuttering in young children. These methods of assessment may lead the way to early identification of young children who are at risk of developing speech dysfluencies and may indicate appropriate intervention techniques for improving the development of speech timing control and preventing stuttering.

Proposed Course: The contract is expected to terminate in July 1983.

CONTRACT NARRATIVE
Communicative Disorders Program
October 1, 1981 through September 30, 1982

OHIO UNIVERSITY, ATHENS, OHIO (NO1-NS-0-2342)

Contractor's Project Director: William Seaton, Ph.D.

Current Annual Level of Support: $31,947

FATHER FLANAGAN'S BOYS HOME, OMAHA, NEBRASKA (NO1-NS-0-2343)

Contractor's Project Director: Ronald Netsell, Ph.D.

Current Level of Support: $21,996

LOYOLA UNIVERSITY AT CHICAGO, CHICAGO, ILLINOIS (NO1-NS-0-2344)

Contractor's Project Director: William A. Yost, Ph.D.

Current Annual Level of Support: $21,167

UNIVERSITY OF CONNECTICUT, STORRS, CONNECTICUT (NO1-NS-0-2345)

Contractor's Project Director: Jay Lerman, Ph.D.

Current Annual Level of Support: $17,178

UNIVERSITY OF HAWAII AT MANOA, HONOLULU, HAWAII (NO1-NS-0-2346)

Contractor's Project Director: James Yates, Ph.D.

Current Annual Level of Support: $11,430

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Date Contracts Initiated: September 15, 1980

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions:

1. What are the information needs of various communicative disorders specialists?

2. Whether various types of specialists in communicative disorders learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?

3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialities?

4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?

5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Methods Employed: Professionals were recruited for involvement as user participants at each MEDLINE center. On admission to the study, each participant completed a pre-use questionnaire. The results of the pre-use questionnaire will indicate the current practices of various professionals and their perceived information needs. User participant training workshops were conducted prior to providing services at each MEDLINE center. Users have unlimited free access to MEDLINE services for 18 months. With each use, users may choose to access information through one of three modes: direct access operating the terminal themselves; working with the technical information specialist at the terminal; or filling out a search request with no involvement in the search process. Data are kept at each center on the modes of access used and corresponding levels of satisfaction. After 18 months of free access, each user participant will complete a post-use questionnaire evaluating their use, level of satisfaction, and preferred search mode of MEDLINE, any changes in their information accessing habits and perceived unmet information needs.

Major Findings: Over 700 user participants are enrolled in the study. The majority of these are speech-language pathologists, audiologists and graduate students. Few had used computerized databases before the project. Personal journal subscriptions and discussions with peers were the most common methods of accessing information prior to the study.

Preliminary data indicate the preferred search mode is conducting a search with the technical information specialist. MEDLINE retrieval results are most satisfactory when users are less familiar with the topic and want to survey a body of literature which they have not been following closely.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists in communicative disorders. The Communicative Disorders Program has focused on meeting the objectives of its Scientific Information Program by upgrading MEDLINE services in communicative disorders. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE and enabling users to have direct access to MEDLINE. The new service model developed by the CDP is much less costly than specialized Information Centers since users learn to access the information directly and are charged only for the online time required and hard copy printout.

Proposed Course: All five contracts wil terminate on March 14, 1983.

MEDICAL UNIVERSITY OF SOUTH CAROLINA (NO1-NS-1-2381)

Title: An Analytical Study of the Auditory Effects of Noise

Contractor's Project Director: John H. Mills, Ph.D.

Date Contract Initiated: July 1, 1981

Current Annual Level of Support: $34,000

Objectives: The purpose of this contract is to conduct a detailed analysis of the auditory effects of noise and to identify areas in need of further investigation.

Methods Employed: With the contributions of 14 scientific experts, a written analysis of completed national and international studies will be made in the following areas: differential diagnosis and measurement of noise-induced hearing loss; individual differences in susceptibility; protection and conservation of hearing; anatomy, physiology and biochemistry; temporary, permanent and asymptotic threshold shifts; noise and other ototraumatic agents; and continuous, intermittent and impulse noise. Areas in need of additional research will be identified in a document with suggested methodologies and procedures for studying the problems.

Major Findings: Over 3,000 studies have been analyzed and ordered according to importance to the scientific knowledge of auditory effects of noise.

Significance to Biomedical Research and the Program of the Institute: Noise-induced hearing loss (NIHL) is one of the few hearing disorders that can be prevented in the American population. This project is intended to identify promising avenues of research that can profitably be pursued to alleviate NIHL.

Proposed Course: Contract is expected to be completed by April 30, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

TUFTS-NEW ENGLAND MEDICAL CENTER (N01-NS-2-2305)

Title: The Prescription of Communicative Devices for Non-Speaking Patients

Contractor's Project Director: Cheryl Goodenough-Trepagnier

Date Contract Initiated: June 30, 1982

Current Annual Level of Support: $248,000

Objectives:

1. To design procedures for determining: a) the cognitive abilities of non-speaking patients with severely handicapping physical and neurological disorders to operate various types of communicative devices, b) the communicative augmentative needs of such patients, c) the cognitive and motor requirements of users for operating various types of communicative devices, and d) the communicative augmentative features of various types of communicative devices;

2. To develop a prescriptive system for selecting the optimal device for an individual patient; and,

3. To conduct a validation study of the prescriptive accuracy of the system for selecting a device which will maximally augment a patient's communicative abilities.

Methods Employed: During the development phase,

1. Objective and reliable patient assessment procedures will incorporate device interface simulators for measuring: the force, range accuracy and speed of movement of the tongue, lips, jaw, fingers, hands, head, etc.; and the range and control of airflow, sucking, blowing, etc. Objective procedures will assess visual and auditory acuity, symbol recognition, language comprehension, scanning, selection and encoding skill, and speech intelligibility.

2. Administration and scoring procedures will be developed for determining patients' augmentation needs including environmental demands, required communication modes and references.

3. Objective and reliable procedures will measure the requirements of users for various types of communicative devices. Formal testing procedures will be applied to determine: the motoric operating requirements including force, range, resolution, duration, latency, and accuracy of various body movements and functions and the sensory, perceptual and cognitive requirements to operate each device.

4. A scoring inventory and procedures for determining the functions of different types of communicative devices will include items parallel to those in the patients' augmentation needs assessment battery.

Major Findings: Not applicable since the contract was just recently initiated.

Significance to Biomedical Research and the Program of the Institute: New communicative devices for the non-vocal are being developed at a rapid rate due to advances in microprocessors. For non-vocal patients to benefit from these advances, patient and device evaluation procedures are required. Objective measurement procedures are needed to initiate research in this field as well as to enable appropriate prescription of devices even when they are not available to the clinician or patient for trial. The system will provide a framework for future device development and should stimulate future research on the needs and treatment of non-vocal patients.

Proposed Course: Phase I will require 27 months for development and pilot testing of the prescription system, while Phase II, the validation study, will require 12 months and should be complete in September 1985.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1982

BOLT, BERANEK AND NEWMAN (NO1-NS-2-2394)

Title: Assessment of High Frequency Hearing

Contractor's Project Director: Kenneth N. Stevens, Sc.D.

Date Contract Initiated: December 8, 1981

Current Annual Level of Support: $159,000

Objectives: The purpose of this contract is to develop and evaluate an electroacoustical device which will reliably and validly measure hearing thresholds in the frequency range of 8,000-20,000 Hz. The ultimate aim will be a system capable of assessing high frequency hearing impairment in humans.

Methods Employed: Measurements are being made on a simple tube with small microphones at both ends to simulate measurements of pressure at the entrance to the ear canal and at the eardrum. Similar measures are being taken on real ears. The measured standing wave patterns are being compared with those obtained from the model system to determine the influence of such factors as non-rigid walls and terminal impedance. Pulses are applied to earphone terminals to obtain samples of pulse response so that preliminary calibration algorithms can be developed. The feasibility of different transducers, microphones and calibration techniques are being explored. Decisions are being arrived at for the calibration signal, transducer position and measurement of canal impedance.

Major Findings: Preliminary results are not yet available.

Significance to Biomedical Research and the Program of the Institute: A reliable and valid means of assessing high frequency hearing in humans will provide a valuable clinical measure for early detection of cochlear damage due to noise-induced and drug-induced trauma. Close monitoring of hearing deterioration is expected to provide evidence for altering the dosage of the damaging agent, either noise or drug, in an effort to protect the patient from further hearing loss.

Proposed Course: Transducers will be developed along with appropriate calibration procedures. A microprocessor-controlled audiological testing system will be designed and constructed. Normative data will be collected on a population of young subjects and a reevaluation of the prototype instrumentation will be conducted. Contract completion date is August 7, 1984.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02185-08 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Characteristics of Dysarthric Speech Associated with Neurologic Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. L. Ludlow	Speech Pathologist	CDP	NINCDS
OTHERS:	C. J. Bassich	Speech Pathologist	CDP	NINCDS
	R. F. Naunton	Otolaryngologist, Director	CDP	NINCDS
	R. Eldridge	Neurologist	IRP	NINCDS

COOPERATING UNITS (if any)

Intramural Research Program, NINCDS

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.35	.25	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The distinctive patterns of speech motor control disturbances (dysarthrias) associated with neuromotor diseases/disorders affecting different regions of the central nervous system are being studied.

An objective system of acoustic analysis has been developed which measures the coordination, timing and rate of different speech gestures, and control of fundamental frequency and speech intensity level. The analysis system was demonstrated valid for differentiating between normal and dysarthric speech and between speech disorders associated with pathologies at different locations in the central nervous system. Measures are being made with a three-dimensional movement transducer of the displacement, velocity and acceleration of lip and jaw movements. The maximum range, rate and onset and offset timing during oral gestures and speech production is being studied in normal speakers and patients with Tardive Dyskinesia, Parkinson's disease, Huntington's Chorea, and Dystonia.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02247-06 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Characteristics and Treatment of Vocal Tics and Language Processing in Gilles de la Tourette Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. L. Ludlow	Speech Pathologist	CDP	NINCDS
OTHERS:	C. J. Bassich	Speech Pathologist	CDP	NINCDS
	R. Polinsky	Neurologist	LCS	NIMH

COOPERATING UNITS (if any)

Intramural Research Program, NIMH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.35	.25	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The vocal tics in Gilles de la Tourette Syndrome are being analyzed to determine the differences in timing control and production between vocal tics and the same productions in normal propositional speech. The relationship between the productions of vocal tics and language formulation deficits in Tourette Syndrome are being examined in an effort to develop an explanatory model for expressive language deficits seen in some of these patients. The family histories and speech and language characteristics of family members of patients with Tourette Syndrome are being examined to develop pedigrees of the familial patterns of speech and language disorders found to occur in 50% of these patients.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02336-05 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cis Platinum and Early Identification of Ototoxicity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Elkins	Audiologist	CDP NINCDS
OTHERS:	A. Pikus	Audiologist	CC
	A. Grimes	Audiologist	CC

COOPERATING UNITS (if any)

Clinical Center Audiology
Radiation Oncology Branch
Division of Cancer Treatment, NCI

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.02	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cisplatinum used in the treatment of testicular and ovarian cancer is known to have ototoxic effects. Cochlear damage is manifest by a high-frequency hearing loss and general difficulty in understanding normal conversational speech. Periodic assessments of pure tone thresholds and suprathreshold speech perception are being conducted to evaluate and relate degree and progression of ototoxicity to drug dosage and frequency of administration.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02337-05 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Effects of Stimulants on the Auditory Processing and Language Skills of Hyperactive, Language Impaired and Normal Subjects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. L. Ludlow	Speech Pathologist	CDP	NINCDS
OTHERS:	J. L. Rapoport	Psychiatrist	IRP	NIMH
	G. L. Brown	Psychiatrist	IRP	NIMH
	C. J. Bassich	Speech Pathologist	CDP	NINCDS

COOPERATING UNITS (if any)

Intramural Research Program, NIMH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.25	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of studies are being conducted to determine the following:

1. The relationships between auditory processing deficits, speech perception skills, attention disorders, and speech and language development in hyperactive boys, with and without learning disorders;
2. The effects of stimulants on the speech, language and communicative skills of language disordered hyperactive boys;
3. Whether auditory processing disorders in hyperactive boys with and without disorders in speech, language and reading respond similarly to the administration of dextroamphetamine; and
4. Whether the effects of stimulant drugs on auditory processing disorders in language impaired children are related to the effects of stimulants on language processing and speech fluency.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02395-04 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	B. F. Haynes	Staff Physician	LCI NIAID
	E. Elkins	Audiologist	CDP NINCDS

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cogan's Syndrome (CS) is characterized by acute nonsyphilitic interstitial keratitis and acute episodes of vertigo, tinnitus and hearing loss. Within 1 to 2 weeks after initiation of corticosteroid therapy, all patients demonstrated improved hearing thresholds for pure tones and supra-threshold speech discrimination results. These patients have been followed an average of 2.5 years; all have only mild-to-moderate hearing impairment in the mid and low frequencies. Three of the patients have been tapered off steroids completely with no subsequent permanent decrement of hearing. Thus, early corticosteroid administration to patients with sudden hearing loss associated with Cogan's Syndrome may preserve auditory function.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02396-04 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Auditory Deficits in Osteogenesis Imperfecta**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	E. Elkins	Audiologist	CDP NINCDS
	E. Gross	Chief, Molecular Structure Section	ERRB NICHD
	J. W. Hansen	Pediatrician, Developmental Biology & Clinical Nutrition Section	NPMB NICHD
	S. Levin	Dept. of Otolaryngology	Johns Hopkins University
	K. Rosenbaum	Dept. of Genetics	Children's Hospital, Washington, D.C.
	D. Rowe	Dept. of Pediatrics	University of Connecticut

COOPERATING UNITS (if any)

LDBA, NIDR; CC, NIH; Molecular Structure Section, ERRB, NICHD; Developmental Biology & Clinical Nutrition Section, NPMB, NICHD; Johns Hopkins University; University of Connecticut; Children's Hospital, Washington, D.C.

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are being developed to delineate the types of hearing losses associated with Osteogenesis Imperfecta (OI). Measurement of middle ear function by tympanometry and acoustic reflexes are being developed to classify penetrance and types of auditory deficits associated with differing forms of this disease.

**[This study is the NINCDS portion of a larger study (CC) entitled: "Collagen Metabolism in Osteogenesis Imperfecta (OI)", of which Dr. Jay R. Shapiro is the Principal Investigator.]

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02440-03 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Development of Acoustic Measurement Tools for Assessing Vocal Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. L. Ludlow	Speech Pathologist	CDP	NINCDS
OTHERS:	R. F. Naunton	Otolaryngologist, Director	CDP	NINCDS
	C. J. Bassich	Speech Pathologist	CDP	NINCDS
	R. Eldridge	Neurologist	IRP	NINCDS

COOPERATING UNITS (if any)

Intramural Research Program, NINCDS and National Naval Medical Center

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.25	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Acoustic measures for the assessment and analysis of phonatory functioning in various types of laryngeal pathology are being developed. Objective noninvasive assessment techniques which can differentiate between normal function and varying degrees of pathology have been completed. Various signal processing algorithms for analyzing frequency and amplitude components of speech waveforms are being evaluated for differential sensitivity to morphological and neurological changes in the larynx. Nasopharyngolarynscopic videotape recordings during connected speech are examined for interpretation of phonatory pathology in various types of disorders including spastic dysphonia and extrapyramidal disorders. Explanatory models of the effects of different laryngeal disease processes on phonatory function are sought to further understanding of the phonatory mechanism.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02441-03 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hearing Assessment in Central Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Elkins	Audiologist	CDP	NINCDS
OTHERS:	A. Pikus	Audiologist	CC	
	R. Eldridge	Head, Clinical Neurogenetics Study	NES	NINCDS

COOPERATING UNITS (if any)
Clinical Center Audiology
Clinical Neurogenetics Studies, NES, ODIR, IRP, NINCDS
Cancer Epidemiology Branch, NCI

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This autosomal dominantly inherited form of neurofibromatosis (NF) usually occurs without the visible stigmata of peripheral NF and is characterized by bilateral acoustic tumors. Complete families are being studied, including children, in order to provide earlier and more accurate diagnoses of tumors. Appropriate and timely medical and audiological management plus counseling are considered for each patient individually.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02464-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in Autism**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	A. Grimes	Audiologist	CC
	J. Rapoport	Physician	NIMH
	J. Rumsey	Psychologist	NIMH
	E. Elkins	Audiologist	CDP NINCDS

COOPERATING UNITS (if any)

Clinical Center Audiology
Biological Psychiatry Branch, NIMH

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Peripheral auditory function is being evaluated in children and adults with Autism. For this difficult-to-test population, differential audiologic assessment is a prerequisite to appropriate long term educational and psychological management. Additionally, the occurrence of auditory deficits in this population has not been clearly defined.

**Part of a cooperative study with NIMH

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02465-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hearing in Peripheral Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	E. Elkins	Audiologist	CDP NINCDS
	A. Grimes	Audiologist	CC
	J. Bader	Clinical Associate	Epidemiology Branch NCI

COOPERATING UNITS (if any)

Clinical Center Audiology
Clinical Neurogenetics Studies, NES, ODIR, IRP, NINCDS
Cancer Epidemiology Branch, NCI

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An interdisciplinary clinic has been staffed for the evaluation of patients with peripheral neurofibromatosis (NF) and their families. Due to the dominant inheritance pattern of the disease, the probability of involvement of offspring is 50-50. The nature and extent of auditory deficits associated with the disorder have not previously been defined in this population. This patient population is being evaluated to provide recommendations for treatment and follow-up by the referring primary-care physicians.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02466-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pediatric Oncology Regimen and Ototoxicity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	A. Grimes	Audiologist	CC
	E. Elkins	Audiologist	CDP NINCDS
	P. Rizzo	Head, Infectious Disease Section Chief, Pediatric Neurological Branch	COP CDT NCI

COOPERATING UNITS (if any)

Clinical Center Audiology
Pediatric Oncology Branch, NCI

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All pediatric oncology patients on the "fever" protocol are given periodic complete audiological analyses to ascertain if certain antibiotics used in prevention or treatment of infection have damaging effects on hearing.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02467-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Auditory Function and Cerebral Vasculitis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	A. Grimes	Audiologist	CC
	E. Elkins	Audiologist	CDP NINCDS
	R. Roberts	Clinical Associate	LCI NIAID

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.15	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This auto-immune disease is associated with auditory and vestibular symptoms. Incomplete information is available on its manifestations in the auditory system. This investigation studies the auditory system deficits in an attempt to identify the most common sites of lesions and to profile the course of this disease within the auditory system.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02468-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in Wegener's Granulomatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	E. Elkins	Audiologist	CDP NINCDS
	A. Grimes	Audiologist	CC
	A. Fauci	Chief, Laboratory of Immunoregulation	LIR NIAID

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This auto-immune disease is often manifest by intractable middle ear diseases in addition to cochlear involvement. The current study evaluates the nature and extent of auditory deficits associated with Wegener's Granulomatosis to determine any effects of treatment on hearing and middle ear function.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER ZO1 NS 02469-02 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Small Cell Carcinoma and Hearing Loss

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC	
OTHERS:	A. Grimes	Audiologist	CC	
	E. Elkins	Audiologist	CDP	NINCDS
	A. Lichter	Chief, Radiation Section	ROB	NCI

COOPERATING UNITS (if any)
Clinical Center Audiology
Radiation Therapy, NIH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Patients with Small Cell Carcinoma of the lung are often treated with chemotherapeutic agents and radiation therapy in combination or sequence. Concern has developed over hearing loss in some patients. Project is designed to help identify which (if either) factor may be causally related to hearing deficits in this patient population.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02470-02 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in an Aging Population*

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC	
OTHERS:	A. Grimes	Audiologist	CC	
	E. Elkins	Audiologist	CDP	NINCDS
	M. Schwartz	Staff Psychiatrist	LNS	NIA
	R. Duara	Senior Staff Fellow	LNS	NIA

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Neurosciences, Gerontology Center,
National Institute on Aging

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An assessment of auditory function of "normal" (healthy aging) subjects is being obtained through an Institute on Aging protocol investigating regional brain metabolism. Subjects are given audiologic assessment test batteries to develop a profile of risk factors for presbycusis.

*Part of larger study with Institute on Aging

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02471-02 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hearing and Neomycin Therapy for Type II Hyperlipidemia**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	A. Grimes	Audiologist	CC
	E. Elkins	Audiologist	CDP NINCDS
	J. Hoeg	Research Associate	MD NHLBI

COOPERATING UNITS (if any)
Clinical Center Audiology
Molecular Disease Branch, NHLBI

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.30	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A double-blind study of the effects of neomycin on hearing is being conducted in patients with Type II Hyperlipidemia. Patients are receiving oral neomycin and dietary regulation in rotation and/or combination. Audiologic examinations establishing baseline data are followed at predetermined increments to be related to the other study variables.

**Part of larger study on Type II Hyperlipidemia and Neomycin Therapy

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02557-01 CDP

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Effects of Penetrating Head Injuries on Speech and Language Functioning

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C. L. Ludlow Speech Pathologist CDP NINCDS

COOPERATING UNITS (if any)

Vietnam Head Injury Project, Walter Reed Army Medical Center, Clinical Investigation Service including D. Dillon, D. Buck, J. Rosenberg and C. Fair

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal is to better understand the brain bases for speech and language functioning. This research is part of a multidisciplinary investigation into the long-term functional and anatomical sequelae of penetrating craniocerebral trauma. Data collection began in 1967 with type of wound, initial neurological presentation, therapy and follow-up examinations. The present phase includes study of (a) anatomical deficits with the use of CT scans and (b) neurological, sensory-motor, hearing, speech, language, and cognitive function. The purpose is to determine (1) whether particular locations of brain lesions following penetrating head injury are associated with specific residual deficits of: strength and range of motion of the articulators; isolated and sequenced oral volitional movements; oral movement and speech syllable repetition; word, phrase and sentence imitation; categorical and temporal order perception for speech sounds; meaningful word and syllable articulation and discrimination; auditory and reading comprehension of lexical, semantic and syntactic information and spoken and written expression of names, phrases, semantic relations and syntactic structures.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02558-01 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Audiologic Findings of Multiple Sclerosis Lymphocyte Depletion Treatment

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	E. Elkins	Audiologist	CDP NINCDS
	A. Grimes	Audiologist	CC
	H. MacFarland	Assistant Chief, Neuroimmunology Branch	NIB NINCDS
	D. McFarlin	Chief, Neuroimmunology Branch	NIB NINCDS

COOPERATING UNITS (if any)

Clinical Center Audiology
Neuroimmunology Branch, NINCDS

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

There is inadequate understanding of 8th nerve dysfunction in multiple sclerosis. This study will determine the role of lymphocyte depletion treatment in the fluctuations of the auditory deficit associated with multiple sclerosis.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02559-01 CDP

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in Alzheimer's Disease*

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Pikus	Audiologist	CC
OTHERS:	E. Elkins	Audiologist	CDP NINCDS
	A. Grimes	Audiologist	CC
	S. Rapoport	Chief, Laboratory of Neurosciences	NIA
	L. Sokoloff	Chief, Laboratory of Cerebral Metabolism	NIMH

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Neurosciences, NIA

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Changes in cognition as well as other neurologic involvement occur during aging and in organic dementia of the Alzheimer type. The changes in the auditory system have not previously been delineated or defined. This study plans to describe the nature and extent of auditory deficits associated with Alzheimer's disease in this population.

*Part of a larger study entitled: Regional Cerebral Glucose Utilization in Organic Dementia of the Alzheimer Type (ODAT)

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02560-01 CDP

PERIOD COVERED
July 1, 1982 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Evoked Potential Correlates of Neurological Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Barry H. Smith	Deputy Chief, Surgical Neurology Branch	SNB	NINCDS
OTHERS:	Ernest J. Moore	Staff Scientist	CDP	NINCDS
	Dan Stowens	Staff Fellow	DMNB	NINCDS
	Susumu Sato	Neurologist	NDP,EB	NINCDS

COOPERATING UNITS (if any)
Surgical Neurology Branch
Clinical Neurosciences Branch
Developmental and Metabolic Neurology Branch

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The aim is to investigate various evoked potential correlates of neurologically normal, and neurologically impaired individuals who exhibit Central Nervous System (CNS) dysfunction as a result of neoplasms and metabolic disorders. A combined evoked potential paradigm is used, capitalizing on short and long latency auditory, somatosensory and visual evoked potentials.

PHS-6040
(Rev. 2-81)

TAB 4 -- FUNDAMENTAL NEUROSCIENCES PROGRAM -- FNP

ANNUAL REPORT
October 1, 1981 - September 30, 1982
Fundamental Neurosciences Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 - September 30, 1982
Fundamental Neurosciences Program
National Institute of Neurological and
Communicative Disorders and Stroke

INTRODUCTION

Basic research in the neurosciences is supported by all four Extramural Programs. However, the Fundamental Neurosciences Program is primarily concerned with those projects which are not obviously disease-related and serve to expand the store of scholarly information in the classic disciplines of neuroanatomy, neurophysiology, neurochemistry, neuropharmacology and neuropsychology. This is the base upon which clinical research is ultimately dependent, not only for information, but for the development of instruments, techniques and methodologies which make applied research possible. The basic research laboratory not only provides the tools for clinical investigation but often the training in scientific methodology as well.

The Neural Prosthesis Program, directed by Dr. F. T. Hambrecht, is an important aspect of FNP activities. It is primarily oriented toward the study and solution of basic problems at the interface between electrodes and nervous tissue, issues which must be satisfactorily resolved before the chronic implantation of devices to compensate for lost sensory or motor capacities. These involve electrode toxicity and materials, parameters of stimulation, corrosion by body fluids, electronic pack encapsulation, and the design and construction of multiple electrodes. This program, one of the few of its kind in the world, is primarily supported through research contracts at the level of about 2.6 million dollars a year.

GENERAL FUNDAMENTAL NEUROSCIENCES

On June 14, 1982 there were 460 regular research grants, 6 new investigator research awards and 12 program project grants in the program (see tables). Neurophysiology and neurochemistry together accounted for about 80% of FNP grants. Twelve percent of the regular research grants supported studies in neuroanatomy with smaller numbers of grants in neurobiology, neuropsychology, neural prostheses and biomedical engineering. Six program projects were in the area of neurophysiology, three were in neurochemistry, two were in neuroanatomy and one in biomedical engineering. It should be emphasized that the FNP only includes basic studies that are not disease or disorder-related and thus constitutes only a fraction of NINCDS support for basic science.

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE REGULAR RESEARCH GRANTS

JUNE 1982

	Number	% of Total	$	% of Total $
Neuroanatomy	58	12.6	4.4M	12.6
Neurophysiology	194	42.2	14.1M	40.3
Neurochemistry	167	36.3	12.8M	36.6
Neurobiology	21	4.6	1.7M	4.9
Neuropsychology	13	2.8	1.0M	2.8
Neural Prostheses and Biomedical Engineering	6	1.3	.5M	1.4
Scientific Information	1	.2	.5M	1.4
TOTALS	460	100.0	35.0M	100.0

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE PROGRAM PROJECT GRANTS

JUNE 1982

	Number	% of Total	$	% of Total $
Neuroanatomy	2	17	1.0M	24
Neurophysiology	6	50	1.5M	36
Neurochemistry	3	25	1.2M	28
Biomedical Engineering	1	8	.5M	12
TOTALS	12	100	4.2M	100

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE NEW INVESTIGATOR RESEARCH AWARDS

JUNE 1982

	Number	$
Neuroanatomy	1	53K
Neurophysiology	2	97K
Neurochemistry	1	38K
Neural Prostheses	2	112K
TOTALS	6	300K

The Neurochemistry of Learning and Memory

One of the strongest attractions of young investigators to the neurosciences resides in the underlying hope that ultimately higher behavioral processes such as learning and memory can be explained in neurophysiological, neurochemical or neuroanatomical terms. Affective behavior, apparently modulated by neurotransmitter and neurohormonal activities, is primarily associated with intrinsic mechanisms that are activated by suitable stimuli and are sometimes identified with certain phylogenetically old brain areas.

"Event-related potentials" recorded from the scalp appear to be correlated with conscious behavior such as attention, decision-making and anticipation. However the origin and underlying neurobiology of these recordings are unknown. Since potentials can be elicited in both humans and animals, there is reason to believe that the relevant brain areas and mechanisms will eventually be identified. An encouraging report on research grant support of these studies is found below.

There is no question that alterations in neural activity are accompanied by metabolic changes, and that the latter are often predominately localized in the areas involved. The use of the 2-deoxyglucose method in conjunction with production of evoked potentials has neatly shown this correspondence which had been assumed for many years. However, energy is required for a great multitude of processes and the role of metabolic change with functional activity may be quite unspecific - perhaps merely a restoration of the status quo ante - replenishment of neurotransmitters and reestablishment of various ionic gradients. Analogously, it is difficult to assess the real meaning of neurochemical changes which occur with "learning" in animals. Over the course of the last 20 years, many experiments have shown an enhanced incorporation of precursors into ribonucleic acid or protein in particular brain regions during and following training. Furthermore, drugs which inhibit ribonucleic acid or protein synthesis, administered just before training, apparently prevent acquisition of the task. However, before the significance of these observations can be evaluated in terms of the chemistry of learning or of the "engram," a number of exacting criteria must be met: changes in the level or turnover of a substance should be anatomically localized, match the time course of the specific phase of memory formation, and not occur when memory formation is inhibited. Removal of the anatomical locus ought to interfere with memory formation and/or recall and neurophysiological recording from the locus of change should detect some form of altered cellular response. Finally, it is desirable to show that observed chemical changes are not related to stress, motor activity or numerous other concomitant processes. Learning may result primarily in a remodeling of synaptic connectivity.

These complex methodological difficulties have led investigators to examine the neurochemical aspect of learning in simpler nervous systems where experimental conditions are more controllable and fewer neurons are involved. Thus, in Aplysia, the sensitization or conditioning of the gill withdrawal reflex is accompanied by increased synthesis of cyclic adenosine monophosphate (cAMP) in the sensory nerve, followed by phosphorylation of the calcium channel and ultimately leading to augmented release of neurotransmitter from the sensory nerve on to the motor nerve. The duration of the conditioned or sensitized response is temporally correlated to the period of higher cAMP levels and increased phosphorylation. Thus, one potential basis for a neurochemical mechanism of learning has been established.

Neuroanatomical Asymmetry in the Human Temporal Lobes

The investigation of neuroanatomical asymmetry in the human temporal lobes and related psychological characteristics continues at McMaster University. Seventy-seven volunteers with cancer have been given psychological tests and, despite some losses, 35 brain specimens have now been obtained. Preliminary results with 12 specimens, correlating macroscopic anatomical variation with some of the cognitive test results and handedness, were presented at a scientific meeting near the end of 1981. Histological analysis has begun on selected cortical areas and some correlations with the microscopic variation now seem possible. A grant proposal to extend this research was submitted recently. This unique research data should provide new clues about the nature of hemispheric specialization in the human brain.

Neurophysiology of Cognitive Processes

Over the past two years, 55 applications have been received in response to this program announcement. By the close of this fiscal year, it is anticipated that 17 awards will have been made in this important area. It is planned to reissue this program announcement during the next fiscal year in order to emphasize the program's continuing interest in promoting research on the biological basis of higher brain functions.

Integration of Autonomic and Somatic Divisions of the Nervous System

In October 1980, FNP issued a Program Announcement "Integration of Autonomic and Somatic Divisions of the Nervous System." Stimulation of this research area was enthusiastically endorsed by the FNP Advisory Committee to remedy a long-standing, unfortunate dichotomy in neurophysiological studies. The separation of the nervous system into somatic and autonomic divisions has obfuscated and neglected constant intimate interrelationships in support of tissue function. During FY 1982, 26 proposals were received of which four were funded.

NEURAL PROSTHESIS PROGRAM

The fruits of past years' efforts were visible on several Neural Prosthesis Program research contracts. Multichannel electrodes designed and fabricated for implantation into the cochleae of human subjects were completed, and under a separate grant in the Communicative Disorders Program were successfully implanted into two deaf individuals. The electrodes were easily inserted, have performed flawlessly, and appear to be well tolerated by the cochlear tissue. Intensive psychophysical testing is now being carried out and the results of this testing will be used to design speech processors which will convert the acoustical waveform of speech to the most appropriate electrical signals to drive the implanted stimulator and electrode arrays. The principal goal of the multichannel cochlear prosthesis is to permit sensory deaf individuals to understand ordinary speech.

Significant progress has also been made on research contracts involving the use of functional electrical stimulation for rehabilitation of quadriplegic individuals. A nine-channel, computer controlled stimulator has been designed and is now operational. This permits control of up to nine separate muscles and is being used to study restoration of both key grasp and pinch grasp in

patients with spinal cord injuries at the C5 and C6 levels. The patients like the computer-controlled system because it reduces the amount of mental concentration that they must exert to utilize the system and because all joint braces are eliminated. The system also permits smoother muscle control with less muscle fatigue. The development of artificial sensory transducers for partial replacement of force and position sensation in the hand has successfully completed feasibility studies and prototype transducers are being fabricated. Over the next few years, these artificial sensors will be incorporated into a closed loop feedback system with microcomputers in the loop. This should permit even more sophisticated control of paralyzed upper extremities by spinal cord injury victims.

Basic research studies for application to neural prostheses have also been productive. For example, research contracts on new materials for electrode construction have demonstrated that iridium metal has a greater margin of safety with respect to electrochemical reactions than platinum which has been the standard noble metal used in most prostheses. High dielectric materials have been deposited on metal substrates and promises a new generation of safe, effective, capacitor electrodes. The adhesion of Parylene to metals has been improved by the use of a new glow-discharge deposited biomaterial.

BIOMEDICAL ENGINEERING

The Biomedical Engineering Program is closely related to the Neural Prosthesis Program. If a contract involves essentially instrument or device development without a significant component of basic or applied research, it is placed in the Biomedical Engineering Program. At the present time, there are two such contracts, one for the development of implanted transdermal stimulators for auditory prostheses, and one for the development of multichannel single unit recording arrays. Progress on the transdermal stimulator has been in the area of increased yields of titanium hermetic packages. The multichannel electrode array contract has just begun, and they are initially studying various substrate materials to form the foundation for the electrode probe. Pure silicon appears to have the strength to pass through brain tissue but may not be strong enough to penetrate the meninges.

The Biomedical Engineering Program also has several projects supported by the grant mechanism which are not monitored as closely as the contracts. Included under grant support is a device to determine axoplasmic flow in vivo, an intracranial pressure monitoring system, a printed circuit electrode array for monitoring neuronal activity in cell cultures, and an instrumentation system for quantitatively measuring changes in motor performance in humans during various treatment modalities.

SCIENTIFIC INFORMATION EXCHANGE

The Neurosciences Research Program

The Neurosciences Research Progran (NRP), until recently part of the Massachusetts Institute of Technology, has transferred its operations to the campus of the Rockefeller University in New York City. For more than 20 years, the NRP has worked to fuse the various disciplines of neurobiology into a single field of neurosciences. Recently a new program has been inaugurated to allow 6-12

scientists at a time to visit the Rockefeller facility for periods from several days to several months and interact with each other and with the University's faculty in the neurosciences. The first activities will be in the areas of the modular organization of the brain, the mechanisms of control of cortical output, the relation between the chemistry and neurophysiology of photoreceptors and the theoretical analysis of functioning nerve networks. Dr. Vernon Mountcastle, Dr. Gerald Edelman, and Dr. Maxwell Cowan will serve as leaders in these new programs.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-3-2307)

Title: Studies of Urinary Bladder Evacuation by Electrical Stimulation

Contractor's Project Director: Emil Tanagho, M.D.

Date Contract Initiated: March 12, 1973

Current Annual Level of Support: $0

Objectives and Methods Employed: Studies are being conducted in animals with upper motor neuron lesions to determine the feasibility of urinary bladder evacuation by electrical stimulation of the sacral spinal roots. Studies are also being carried out on methods of preventing urinary incontinence.

Major Findings: This contract expired in March 1982 and major effort was placed on summarizing data from animal studies over the last nine years and preparing a final report.

Significance to Biomedical Research and to the Program of the Institute: The restoration of the ability of persons with neurogenic bladders to empty their bladders voluntarily is a long-range goal of this work and would reduce urinary tract infections that are a major cause of death in paraplegics and quadriplegics. The problem of urinary incontinence is of both social and medical significance, especially in the geriatric population.

Proposed Course of Contract: This contract terminated in March 1982. The Project Director was successful in obtaining a NINCDS grant to evaluate the techniques of bladder evacuation and control of incontinence by electrical stimulation in humans. This grant started April 1, 1982.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: EIC LABORATORIES (NO1-NS-9-2315)

Title: Safe Procedures for Electrical Stimulation of the Nervous System

Contractor's Project Director: Barry Brummer, Ph.D.

Date Contract Initiated: August 28, 1979

Current Annual Level of Support: $0

Objectives and Methods Employed: The electrochemical processes that occur at the electrode-electrolyte interface and methods of reducing undesirable reactions are being studied. Techniques such as atomic absorption spectrophotometry, and cyclic voltammetry are used to analyze the simulated extracellular fluid in which electrodes have been pulsed with the goal of developing electrodes and stimulus regimens to reduce undesirable electrochemical reactions.

Major Findings: Studies of the corrosion resistance of iridium compared to platinum and platinum-iridium alloys continues to show the superiority of pure iridium. This is due to the high charge carrying capacity of the activated iridium surface. Biphasic pulsing of iridium in saline solutions for periods up to seven days has little or no effect on the stability of activation. Initial results indicate that activation of the iridium surface extends the useful charge injection limits for anodic pulses as much as tenfold. These tests were repeated with the same results in human cerebrospinal fluid.

Significance to Biomedical Research and to the Program of the Institute: Development and evaluation of safe stimulating techniques for use in neural prostheses are major goals of the Neural Prosthesis Program of the Institute.

Proposed Course of Contract: This contract will expire during this fiscal year. Proposals for competitive renewal have been received and negotiations for a new contract are presently in progress.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: ELECTROCHEMICAL TECHNOLOGY CORPORATION (NO1-NS-9-2316)

Title: Electrochemical Studies

Contractor's Project Director: Dr. Theodore Beck

Date Contract Initiated: December 1, 1979

Current Annual Level of Support: $120,000

Objectives and Methods Employed: New stimulation electrodes based on ion selective membranes are being developed and fabricated.

Major Findings: The pH changes which result from biphasic pulsing of small electrodes at high charge and current densities were evaluated. At a current density of 1 ampere/cm^2, pH values of 6-10 can be produced at the surface of an electrode immersed in extracellular fluid. A technique has been developed for applying ion selective membranes to electrodes that is based on dipping electrodes in a viscous, partially polymerized solution. MMA/MAPTAC polymers were found to maintain their transference numbers and physical properties when submitted to aging in normal saline for 154 days. The conductivities of these polymers decrease slowly with age but are still well above their required minimum. A mathematical analysis of the temperature elevation that might occur with miniature intracortical metal stimulating electrodes was completed. In essence, electrodes as small as 5-10 microns in diameter and exposed length produce no significant temperature elevation in the extracellular fluid at distances greater than about 1 micron from the electrode.

Significance to Biomedical Research and to the Program of the Institute: Neural prostheses that utilize functional electrical stimulation require safe techniques for long-term neuronal activation and inhibition. This work will provide a better understanding of the electrochemical factors involved and will develop new electrodes based on these findings.

Proposed Course of Contract: This contract will expire in December 1982. A renewal contract has been advertised and proposals received.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: HUNTINGTON MEDICAL RESEARCH INSTITUTES (NO1-NS-0-2319)

Title: Safe Methods of Electrical Stimulation

Contractor's Project Director: William Agnew, Ph.D.

Date Contract Initiated: March 1, 1980

Current Annual Level of Support: $283,381

Objectives and Methods Employed: The histopathological effects of long-term electrical stimulation of the nervous system in animals are being studied with various electrode designs, stimulus wave forms, and stimulus parameters. Major emphasis is on intracortical electrodes and peripheral nerve stimulating electrodes. During stimulation, ion-sensitive electrodes are used to monitor changes in extracellular ion concentrations. When long-term stimulation is completed, the tissues surrounding the electrodes are examined using both light and electron microscopy.

Major Findings: Ion-selective microelectrodes are used to monitor changes in the concentration of potassium and calcium in the extracellular compartment of the cerebral cortex during up to four hours of continuous electrical stimulation of the cortical surface. At stimulus charge densities that induce minimal localized histological changes in the tissue, extracellular potassium underwent only a transient increase at the beginning of stimulation followed by a rapid return to the prestimulation concentration. The extracellular calcium was unaffected. At a higher charge density that is known to produce histological damage, there was a rapid transient increase in extracellular potassium followed by a more gradual return to a plateau level, slightly above the prestimulus value. Extracellular calcium decreased then increased at a depth 100 microns below the surface of the cortex but underwent an increase followed by a slow decrease in the middle layers (750 microns). Studies of the effects of intracortical electrical stimulation of the cerebral cortex of cats with charge balanced, rectangular pulses for a continuous period of 24 hours have shown that moderate to severe neural damage only occurs after stimulation with charge densities of at least 400 microcoulombs/cm^2 per phase. There was no evidence of erosion of electrode tips following stimulation at this level as assessed by scanning electron micrographs of the electrodes. Histological evaluation of electrode tracts indicated that implantation of passive electrodes induced the formation of a connective tissue sheath, and in some instances, minimal neural damage at the exposed tip. Studies of the Avery cuff electrode implanted around sacral nerve roots in dogs have indicated, following ten months of implantation, that there is essentially no change in function, and histopathological evaluation revealed normal appearing nerves. This is true for both control nerves and nerves stimulated at levels which produce bladder evacuation in dogs.

Significance to Biomedical Research and to the Program of the Institute: These studies are important for determining the safety and efficacy of various forms of neural stimulation utilized in neural prostheses for the neurologically handicapped. In addition, new surgical and neurophysiological techniques are being developed which are proving valuable to neurosurgeons and neurophysiologists in other laboratories and clinics.

Proposed Course of Contract: This contract is in the third year of a three-year contract. A competitive renewal is expected.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: CASE WESTERN RESERVE UNIVERSITY (N01-NS-0-2330)

Title: Study of Intramuscular Electrical Stimulation of Muscle

Contractor's Project Director: J. Thomas Mortimer, Ph.D.

Date Contract Initiated: June 27, 1980

Current Annual Level of Support: $333,702

Objectives and Methods Employed: The use of electrical stimulation of the neuromuscular system in animals and humans for artificial control of muscle and generation of purposeful movements is being studied. The ultimate goal is to restore function to the upper extremities in patients paralyzed as the result of spinal cord injuries.

Major Findings: (1) A nine-channel, computer controlled stimulator has been developed and is now in regular use in the patient laboratory. The hardware development was supported by the National Institute of Handicapped Research (NIHR) and the software development by this contract. (2) Piecewise, linear modulation of stimuli are used to generate single axis control for both of two hand-grasping modes and for implementing a finer control of palmar prehension grasp. (3) A digital controller has been designed to provide regulated compliance of stimulated muscle. (4) Second generation force transducers have been fabricated and successfully passed sensitivity and stability tests. (5) Relationships between stimulus parameters and excitation of different diameter myelinated nerve fibers in peripheral nerves have been determined.

Significance to Biomedical Research and to the Program of the Institute: The techniques being investigated are restoring lost function to paralyzed individuals.

Proposed Course of Contract: This is the third year of a three-year contract. A competitive renewal is anticipated.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF MINNESOTA (N01-NS-0-2332)

Title: Study of the Effects of Electrical Stimulation of the Cerebellum

Contractor's Project Director: Dr. James Bloedel

Date Contract Initiated: September 29, 1980

Current Annual Level of Support: $92,769

Objectives and Methods Employed: The effects of cerebellar stimulation on primate models of spasticity and movement disorders are being evaluated. The neurophysiological mechanisms and anatomical pathways associated with these effects are also being examined.

Major Findings: Unilateral decortication encompassing the left motor cortex (area 4 in the left premotor cortex and area 6 in Rhesus monkeys) results in extensive co-contraction of the biceps and triceps of the right arm during trained voluntary movements, but the trajectories in individual components of the movements have remained the same. Electrical stimulation through four bipolar electrodes implanted in the right interposed and dentate nuclei modifies the trajectory of the movement. Specifically, stimulation of the anterior interposed nucleus during the turnaround period in the movement results in the animal missing the start position on the return path which is evidence of stimulation-induced dysmetria. New data indicate that the effects of dentate stimulation on the characteristics of the stretch reflex recorded in the gastrocnemius and tibialis anterior muscles can be graded over a range of stimulus intensities and that the threshold for effecting the stretch reflex of the extensors occurs at a slightly lower threshold than the stimuli required to effect the stretch reflex of the flexor muscles. These effects were dependent on the phase of the stretch during which stimuli were applied.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the neurophysiological mechanisms, if any, by which cerebellar stimulation modifies normal movement and movement disorders.

Proposed Course of Contract: This investigation is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF UTAH RESEARCH INSTITUTE (N01-NS-0-2335)

Title: Transducer Development and Evaluation of Sensory Feedback

Contractor's Project Director: Andrew A. Schoenberg, Ph.D.

Date Contract Initiated: August 1, 1980

Current Annual Level of Support: $220,849

Objectives and Methods Employed: The possibility of providing artificial pressure, force, slip, and position information to quadriplegic patients has not been explored because of lack of suitable transducers. This research will develop such transducer systems and evaluate them in a simulated model of a paralyzed hand that is controlled by functional neuromuscular stimulation.

Major Findings: For finger location sensing, longitudinal mode vibration of the PVF_2 material is now used instead of the thickness mode vibration to get a higher transmission power and receiver sensitivity. Electronic circuitry has been developed for the force transducers.

Significance to Biomedical Research and to the Program of the Institute: This research is part of a multidisciplinary approach to the restoration of lost function in paralyzed individuals. Restoration of sensation could also be useful to individuals with congenital absence of sensation or with severe burns.

Proposed Course of Contract: This work is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: STANFORD UNIVERSITY (N01-NS-0-2336)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Robert White, Ph.D.

Date Contract Initiated: September 15, 1980

Current Annual Level of Support: $214,860

Objectives and Methods Employed: State-of-the-art microelectronic techniques are being applied to the design and development of second generation multi-electrode arrays for stimulation of the eighth nerve. These electrodes will be used for the evaluation of the feasibility of multichannel auditory prostheses.

Major Findings: Metal-polyimide adhesion has been successfully achieved by vacuum-evaporating titanium and platinum onto the activated surface of the polyimide. These have survived 14-hour boiling in deionized water followed by a tape test. A stiffener wire embedded into the Silastic carrier of a thin-filmed scala tympani electrode has improved the mechanical properties. Using such a configuration, a number of non-traumatic scala tympani implants have been made in cat cochleae.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve may provide a means of communication for sensory deaf individuals. The NINCDS is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This investigation is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (NO1-NS-0-2337)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Michael Merzenich, Ph.D.

Date Contract Initiated: September 1, 1980

Current Annual Level of Support: $188,083

Objectives and Methods Employed: The electrical and mechanical properties of the scala tympani are being studied and on the basis of these results, multichannel stimulation electrode arrays are being developed which are suitable for stimulation of the eighth nerve in humans.

Major Findings: Two sixteen electrode, eight-channel scala tympani electrode arrays which were designed and developed under this contract have been fabricated and inserted into two human volunteers (with the support of a separate grant in the Communicative Disorders Program). Special instruments were designed for implantation of these devices and include a special forked cup forcep, a depth limited trephine, and a cable passer for quickly passing the electrical cable from the electrode array beneath the scalp to the percutaneous connector. Also designed is a novel surgical disconnect plug which is being patented.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve in the scala tympani may provide a means of communication for sensory deaf individuals. This Institute is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This investigation is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: STANFORD UNIVERSITY (NO1-NS-1-2354)

Title: Transdermal Stimulation Electronics for Auditory Prostheses

Contractor's Project Director: Robert L. White, Ph.D.

Date Contract Initiated: July 1, 1981

Current Annual Level of Support: $211,367

Objectives and Methods Employed: Design, development, and fabrication of transdermal stimulators to be used in the evaluation of multichannel cochlear implant auditory prostheses.

Major Findings: For over one half of the contract year, the integrated circuits laboratory at Stanford University was not in operation due to remodelling and the need for changes to meet government regulations. During this down period, considerable effort was expended on designing and fabricating the next generation eight-channel implantable stimulators. A stagger-tuned system was developed to reduce the dependence of transmission voltage gain upon coil coupling. This has been completed and a model fabricated. Results indicate that a voltage gain of .71±12 percent can be maintained over a variation of coupling coefficient from 0.2 to 0.6 and over a variation in load resistance from 260 ohms to 5000 ohms. Measurements of tissue loss at 20 megahertz were completed. The losses were found to be negligible. A new design of the voltage regulator section of the implant was completed and is compatible with the proposed CMOS processing planned. It has a low current consumption (100 microamps) and can produce regulated current and output voltage with only one volt dropped across the regulator itself. A minor change in the transmission coding scheme makes it possible for new transmitter units to operate as either an eight-channel monopolar or four-channel biopolar stimulator without hard-wire changes. Redesign of the oscillator-transmitter system has brought the power consumption down from 500 milliwatts to 160 milliwatts. A technique has been developed for attaching miniature platinum-iridium wires to tantalum feedthroughs based on microwelding.

Significance to Biomedical Research and to the Program of the Institute: The Institute is presently supporting, under the grants mechanism, the evaluation of multichannel auditory prostheses. This contract will provide electronic stimulators to several of these grantees.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: EIC LABORATORIES (NO1-NS-1-2356)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Barry Brummer, Ph.D.

Date Contract Initiated: September 1, 1981

Current Annual Level of Support: $176,919

Objectives and Methods Employed: Improvements in the charge storage capability per unit volume and the current density output capability of capacitor electrodes suitable for intracortical stimulation of neural tissue are the major objectives. Prototype capacitor electrodes will be fabricated and supplied to other investigators.

Major Findings: Films of $BaTiO_3$ were made by RF sputtering. Using Auger spectra, they were compared with the polycrystalline $BaTiO_3$ target and shown to have a similar stoichiometry. Preliminary ac bridge measurements of the capacitance of the as-deposited and heat treated films showed that the dielectric constant of the heated films was increased by an order of magnitude over non-heated films. The increase is expected if the heat treatment converts the amorphous $BaTiO_3$ film to the polycrystalline modification. Titanium capacitor electrodes which were fabricated under this contract were supplied to NIH for *in vivo* testing in monkeys. During stimulation, the titanium oxide dielectric became very leaky. Although this tended to reverse itself between stimulation periods, the electrodes were considered unacceptable. Because of this and the fact that the titanium electrodes showed no significant advantages over tantalum capacitor electrodes, no further work on titanium capacitor electrodes will be carried out. Emphasis will be placed on high dielectric constant materials such as $BaTiO_3$.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of neural tissue.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF MISSOURI (NO1-NS-1-2382)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Allen Hahn, Ph.D.

Date Contract Initiated: September 30, 1981

Current Annual Level of Support: $217,930

Objectives and Methods Employed: Development of new biomaterials for use as implant encapsulants, primers, and lead insulators. In a single reactor, glow discharge polymers are being used as primers for insulators such as Parylene.

Major Findings: Attempts to use argon cleaning of substrates have failed because the argon causes sputtering of polymers deposited on the chamber walls. This resulted in a thin layer of polymer being deposited on substrates rather than the surface being removed from the substrates. This is also true for other materials within the chamber such as aluminum as demonstrated by Auger spectroscopy in the first few angstroms of the substrate. Studies of the degree of completeness of polymerization of Parylene films have shown that there is less than 1 percent of dimers and other oligomers in the synthesized Parylene. Tensile pull tests have shown that plasma treatment of exposed Parylene surfaces can provide enhancement of epoxy adhesion. Studies on mechanical flex testing of both smooth and roughened surfaces substantiate the fact that adhesion of Parylene is improved with an increase in substrate surface roughness. As the temperature of Parylene C synthesis chamber is lowered, there is a deterioration of the mechanical properties and the morphology of the polymer chains. Preliminary biocompatibility studies with glow discharge polymerized methane show minimal reactions except for some minor movement artifact effects.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved encapsulation and sealing systems to prevent their access to the implants will be useful not only to neural prostheses, but to other artificial organs that involve implanted electronics.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: UNIVERSITY OF MICHIGAN (NO1-NS-1-2384)

Title: Multichannel, Multiplexed, Intracortical Recording Electrode Arrays

Contractor's Project Director: Dr. Ken Wise

Date Contract Initiated: September 25, 1981

Current Annual Level of Support: $189,000

Objectives and Methods Employed: Develop miniature, multichannel, multi-electrodes for recording single-unit electrical activity from the cerebral cortex at precisely known depths. State-of-the-art photolithographic and electron beam lithographic techniques will be used in conjunction with custom-designed, monolithic integrated circuits to produce the electrode arrays.

Major Findings: This contract has just begun and emphasis has been placed on determining the best substrate material for the electrode array. Design of the electronic circuitry that will be part of the probe structure has been initiated. Silicon has been evaluated as a substrate material. It has the mechanical strength to pass through cortical tissue but does not appear to be strong enough to penetrate the meninges.

Significance to Biomedical Research and to the Program of the Institute: The ability to record simultaneously from different single neurons in a cortical column will provide information as to the functional significance of cortical columns in the cerebral cortex. Eventually, it is hoped that single-unit activity can be recorded for long periods of time and utilized as command signals for neural prostheses.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: HUGHES AIRCRAFT COMPANY (NO1-NS-1-2391)

Title: Adhesion Studies

Contractor's Project Director: Ms. Danute Basiulis

Date Contract Initiated: September 30, 1981

Current Annual Level of Support: $159,983

Objectives and Methods Employed: A study is being carried out on adhesion of various insulators to substrates which are being considered for use in neural prosthetic implants. The goal is to improve adhesion and prevent water condensation between sealants and substrates.

Major Findings: Measurements of the moisture barrier capabilities of chemically vapor deposited films of PHOTOX SiO_2, PHOTONITRIDE PLASMA-NITRIDE on interdigitated, double tract, parallel, serpentine pattern of aluminum films was completed. An additional influence of a 20 volt dc bias between parallel films during humidity exposure was also monitored. After ten days of exposure to humidity, all the bias test vehicles failed by having an open circuit develop in one or the other of the aluminum films. The test vehicles that were not subject to bias had an 80 to 100 percent survival rate. A new method of removing Parylene from electrode tips has been developed which is based on plasma etching.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved sealing systems to prevent the access of water and sodium ions to the implants will be useful not only to neural prostheses, but to the development of all artificial organs which involve implanted electronics.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: GINER, INC. (NO1-NS-2-2392)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Harry Lerner, Ph.D.

Date Contract Initiated: November 1, 1981

Current Annual Level of Support: $141,030

Objectives and Methods Employed: Research on methods of increasing the charge storage capability per unit volume and the current density output capability of capacitor electrodes that are suitable for stimulation of neural tissue is being carried out.

Major Findings: Small, porous, sintered tantalum electrodes 100 microns in diameter and conically tipped were successfully fabricated using a modified slurry dipped method. These electrodes have a specific capacitance of over 250 nanofarads/mm^2 compared to electrolytically roughened electrodes which had a specific capacity of 150 nanofarads/mm^2. The porous structure occupies about 60 percent of the total volume based on scanning electron microscopic analysis. Studies of a tantalum-titanium alloy indicate that it does not offer any advantage over pure titanium in terms of both capacitance and leakage current. Attempts to electrolytically etch tantalum wires to increase surface roughness were limited by the fact that only the superficial surface (less than 5 microns deep) of the electrode was roughened by this technique.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of central nervous system tissue.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: MCMASTER UNIVERSITY (NO1-NS-2-2396)

Title: Neural Control of the Urinary Bladder

Contractor's Project Director: Andrew Talalla, M.D.

Date Contract Initiated: April 26, 1982

Current Annual Level of Support: $121,500

Objectives and Methods Employed: The feasibility of sacral root stimulation for evacuation of the urinary bladder in human subjects with neurogenic bladders will be determined. Electrodes will be placed on the appropriate sacral nerves and connected to implanted stimulators. Urologic status of these patients will be determined and any complications noted.

Major Findings: There are no major findings as this contract has just been initiated.

Significance to Biomedical Research and to the Program of the Institute: The restoration of the ability of persons with neurogenic bladders to empty their bladders voluntarily is a long-range goal of this work and would reduce urinary tract infections that are a major cause of death in paraplegic and quadriplegic individuals.

Proposed Course of Contract: This work is in the first year of a three-year contract.

TAB 5 -- NEUROLOGICAL DISORDERS PROGRAM -- NDP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 - September 30, 1982

NEUROLOGICAL DISORDERS PROGRAM
NATIONAL INSTITUTE OF NEUROLOGICAL
AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF REPORT

The Annual Report has four sections. The first section is a brief administrative summary of the program. The second section is a report from the Office of the Director, NDP with eight subsections. The third and fourth sections are reports from the Epilepsy and Developmental Neurology Branches respectively.

PROGRAM SUMMARY STATEMENT

The Neurological Disorders Program (NDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) consists of the Office of the Director, the Developmental Neurology Branch and the Epilepsy Branch. The Program has responsibility for the support of research directly or indirectly related to all of the medical neurological disorders except for stroke. The eight categories into which these disorders are grouped for administrative purposes are as follows:

Convulsive and Related Paroxsymal Disorders
(administered within the Epilepsy Branch)
Demyelinating and Sclerosing Disorders
Infectious Diseases of the Nervous System
Muscular and Neuromuscular Disorders
Neural Aspects of Learning and Behavior
Neurological Disorders of Aging
Other Neurological Studies
Neurological Disorders of Early Life
(administered within the Developmental Neurology Branch)

Grant Activity

The major mechanism of Program support is the investigator-initiated research grant application. During FY 1981, the Program initiated seven program announcements designed to encourage research in areas where it was felt that additional effort was appropriate.

Four of the announcements were to strengthen further the Program's emphasis on neurological disorders of the pediatric age group; i.e., Neurological Abnormalities associated with Learning Disorders, Neural Tube Defects, Neonatal Brain Disorders, and Neurobiology of Autism.

Research momentum in the Epilepsy Branch has been maintained with three program announcements to encourage investigation into basic mechanisms of epileptogenesis, relation of hormones to epilepsy, and development of small animal models for screening of antiepileptic drugs.

Highlights of grant supported research findings are presented in the subsections of the reports of Office of the Director and the Branches.

Contract Activity

The bulk of the Program's contract funds are used by the Epilepsy Branch to support their continuing program to develop more effective antiepileptic drugs. Promising compounds are moving through the Epilepsy Branches Chronic Toxicity Screening Program. These activities are described more fully in the report of the Epilepsy Branch.

The analysis and publication of the National Collaborative Perinatal Project (NCPP) data by the Developmental Neurology Branch nears completion with the publication of one monograph and numerous articles in FY 1982. Four additional monographs are in various stages of preparation. An RFP has been issued to create a users guide to the NCPP files so that interested members of the general biomedical public may have free access to the original data. These activities are more fully described in the report of the Developmental Neurology Branch.

Direct Operation Activities in FY 1981

1) Program Advisory Committee

The Neurological Disorders Program has an Ad Hoc Advisory Committee of outside experts to provide guidance for its activities. The Committee members are:

Robert G. Grossman, M.D.	Baylor College of Medicine
Robert J. Gumnit, M.D.	St. Paul-Ramsey Medical Center
Richard T. Johnson, M.D.	The Johns Hopkins University
Seymour Levine, M.D.	New York Medical College
Joseph B. Martin, M.D., Ph.D.	Massachusetts General Hospital
Dominick P. Purpura, M.D.	Albert Einstein College
J. Murdoch Ritchie, Ph.D., F.R.S.	Yale University
Joseph J. Volpe, M.D.	St. Louis Children's Hospital

One meeting was held in FY 1982.

3) NDP Sponsored Workshops and Conferences

In addition to several workshops and conferences for which the Neurological Disorders Program provided financial support by the grant mechanism, the Program also provided substantial staff input into organizing and conducting a meeting to explore the need for support of antibody or tissue banks.

4) Study of Huntington's disease in Venezuela

In March 1982, the Program sponsored a field trip to Maracaibo, Venezuela, in order to obtain family histories as well as tissue samples from families with Huntington's disease. One extensive genealogy was constructed, and about 150 new tissue samples were returned to the United States for storage at the Massachusetts General Hospital and the Camden National Repository. This project is described further in the "Neurological Disorders of Aging" report.

CONTRACT NARRATIVE
Neurological Disorders Program
October 1, 1981 - September 30, 1982
NO1-NS-9-2320

Title: A Research Roster for Huntington's Disease Patients and Families.

Contractor's Project Director: P. Michael Conneally

Current Annual Level of Funding: $118,997

Objectives: To establish a National Research Roster of patients with Huntington's disease (HD) and their families. This roster will serve as a national source of information for physicians and scientists interested in locating Huntington's disease patients and families willing to participate in experimental studies into the diagnosis, etiology and treatment of this disease. Also to furnish statistical and demographic data on families collected.

Major Accomplishments: The HD Research Roster was established at Indiana University in September, 1979. Its contractor has developed two questionnaires: A family history form for entering pedigrees and an in-depth questionnaire for affected individuals. A third data form for those at risk is being developed.

Roster personnel have made an intense effort to contact families across the country. In the United States, 548 separate families (comprising 855 individuals living and dead) have been entered, representing 47 states. 705 Affected Questionnaires have been received. Families from Canada, Greece, and Venezuela add more than an additional 2,000 people to the Roster data base.

A brochure has been developed for distribution at scientific meetings. Notices in journals, booths at professional society meetings, and other forms of advertisement are being used to stimulate increased scientific utilization of the roster now that families are available. Issues of confidentiality have been sensitively handled and the response to the Roster from scientists and families has been positive. A growing list of investigators are utilizing the Roster to retrieve statistical data or make contact with research subjects. Roster data have led to a major new hypothesis for understanding age of onset and the inheritance pattern for juvenile HD, developed in a paper now in press.

The Roster has also computerized over 2,000 individuals belonging to an exceedingly complex HD kindred in Venezuela and is serving as a data clearing-house for molecular geneticists using tissue samples from pedigree members.

Proposed Course of the Contractor: This program is under the surveillance of an NINCDS project officer and performance is under continued review. The original Roster contract expires September 30, 1982. A Justification for Noncompetitive Procurement was submitted and approved, and a new Roster contract will be negotiated for an additional three years of support.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01163-20 NDP

PERIOD COVERED: October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Selected Maternal Risk Factors and Congenital Cardiovascular Anomalies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Bajda	Medical Consultant (Pediatrician)	OD NDP NINCDS
Other:	A. Naylor	Research Geneticist	DNB NDP NINCDS

COOPERATING UNITS (if any)

Birth Defects and Genetic Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH

Office of the Director, Neurological Disorders Program, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study, using data from the NINCDS Collaborative Perinatal Project, investigates the relation of selected factors which may affect the mothers during pregnancy, and possibly cause congenital heart defects in the children. Observations on about 47,000 pregnancy records provide case and control data for analysis. Some 486 children have been identified as having definite congenital cardiac anomalies. These include cardiac conditions which are part of known syndromes but exclude children suspected of having ventricular septal defects who are reported without cardiac defect at the one-year examination and thereafter. Preselected maternal risk factors noted in the pregnancy records for the mothers of 392 children with definitely defined congenital heart anomalies are compared with control data matched for maternal age, race, date of LMP, and geographical location (institution).

This project has been discontinued.

The program supports research in the neurobiology of degenerative diseases such as Parkinson's disease, Huntington's disease, Alzheimer's disease, Related Disorders, such as tardive dyskinesia, and General Studies. Grants on Parkinson's disease primarily follow a biochemical strategy (34 grants, $4,400,000). A broadbased approach ranging across genetics, biochemistry, and psychology is being pursued in the Huntington's disease program (14 grants, $2,400,000). Research on Alzheimer's disease and other dementias of aging, which pose major public health problems, is gradually increasing (20 grants, $2,000,000). The program in General Studies includes work on the structural and functional alterations of the normal and pathological aging nervous system, (10 grants, $600,000). The Related Disorders program research projects, which have pharmacological implications, (4 grants, $300,000) focus especially on tardive dyskinesia. The total program contains 82 active research grants totalling $9,800,000.

Parkinson's Disease and Parkinsonism

Parkinson's disease, the most common form of Parkinsonism, is a common illness of middle life. About one-half million people in the United States or about 1% of the population over age 50, are affected by this disease. Prevalence and incidence rates are about the same in all races and throughout the world where good epidemiological studies have been conducted. Men and women are equally affected.

The primary cause of Parkinson's disease remains a mystery. Dopamine (DA) containing neurons in the substantia nigra die, causing a depletion of this important neurotransmitter. Gradually, clinical signs of tremor, rigidity, and bradykinesia begin to appear, becoming more severe as time passes. Many patients suffer gradually diminished intellectual faculties. The symptoms of Parkinsonism can also result from neuroleptic administration, as a postencephalitic sequelae, from arteriosclerosis and from a variety of diseases and intoxications.

The majority of grants on Parkinson's disease focus on the biochemistry of the illness and the ways in which neurotransmitter systems transmit messages in the brain areas most affected. It is not surprising that the biochemistry of this disorder should preoccupy scientific attention since discovery of the deficiencies of dopamine in Parkinson's disease patients led to breakthroughs in our understanding of neurochemistry and pharmacology in brain disorders in general.

Clinical Studies

Now that the initial excitement of discovering that decreased dopamine stores leads to Parkinsonian symptomatology has subsided, it has become increasingly apparent that administration of L-dopa to increase endogenous dopamine stores is not sufficient to treat the disease completely. Unpleasant side effects and an erratic effectiveness of the treatment, known as the "on-off" phenomenon, have pushed scientists to seek new treatments. Many of these compounds act in concert with L-dopa to increase its potency; others mimic its action.

Investigators at New York University have had a long-standing research program dedicated to discovering new treatments for Parkinsonism. They have had some success using dopamine agonists such as bromocriptine and lergotrile. Both drugs were effective in relieving tremor in Parkinsonian patients and also in VMT-lesioned monkeys, but lergotrile was shown to have significant hepatotoxic effects. Several ergoline derivatives were evaluated for their dopamine agonist activity in animals, but only two drugs, pergolide and lisuride, were shown to be potent DA agonists and long acting agents in the experimental animal models. Preliminary clinical studies with pergolide are positive. Studies suggest that pergolide has a high affinity for pre- and postsynaptic DA receptors, while its partial ergoline analogue has a high affinity for the presynaptic, but not for the postsynaptic DA receptors. The data also suggest that dopamine synthesis in vitro and in vivo may be regulated by different presynaptic DA receptors. The nigral graft model and the possible role of epinephrine systems in DA-mediated behaviors is also being explored.

New compounds will hopefully be added to the drug armamentarium currently available for treating Parkinsonism. An investigator at St. Louis University has identified a group of carboxylic acid derivatives of tetrahydroisoquinoline compounds which have important pharmacologial effects on an endogenous opiate system on neuroendocrine systems, and on the neurotransmitters dopamine and epinephrine. Working on a theory that the adverse side effects of L-dopa treatment, including the debilitating "on-off" phenomena, stems from the conversion of dopamine to o-methyldopamines, investigators at the Columbia Presbyterian Hospital propose to study the action of catechol-o-methyl transferase (COMT) inhibitors to prevent this conversion and serve as an adjunct treatment in Parkinsonism.

Pharmacological tools are not the only resources available for the clinical treatment of Parkinson's disease. A scientist at the University of Wisconsin is examining the clinical efficacy of a combined program of stress management and EMG biofeedback relaxation techniques to reduce Parkinsonian symptoms. Biofeedback training will enable the patient to manage specific problems, such as rigidity, tremor, and "freezing", while learning to manage stress will help the patient minimize situations which exacerbate symptoms. The study promises to develop useful adjunct therapy with no pharmacological side effects to interfere.

Centers

At the University of Colorado a "Center for the Study of Basal Ganglia Disorders and Neurotransmitter Function" has had a continuing and productive history and serves as an example of the work pursued in these projects. Neuropharmacological, neurochemical, electrophysiological and immunocytochemical techniques are used to explore normal and abnormal functioning of the basal ganglia. The major thrust of the program is a multidisciplinary study of neurotransmitters and neuromodulators in the central nervous system (CNS) with major emphasis on the basal ganglia and the nigrostriatal dopamine pathway. Four research programs examine the neurochemical and electrophysiological changes in basal ganglion function brought about by acute and chronic nerve stimulation and agonist or antagonist drug administration. Special attention is given to the roles of presynaptic and postsynaptic receptors. The effects of chronic drug administration and, as a related theme, neuronal plasticity are the focus of a number of research projects. Studies include aspects of neuronal growth,

differentiation and regeneration, and the influences of calcium dependent regulator proteins, glycoproteins and growth factors on these processes. Neurotransmitter biosynthetic enzymes are viewed as indices of neuronal growth and development.

Tyrosine hydroxylase from rat pheochromocytoma has been purified to homogeneity and its physical and kinetic properties have been characterized by the investigator at this center. The holoenzyme has a molecular weight of approximately 240,000 daltons and consists of four subunits which appear to be identical or nearly identical. The enzyme is phosphorylated by cyclic AMP-dependent protein kinase and enzyme activation is well correlated with phosphorylation. An immunocytochemical procedure was developed for localizing tyrosine hydroxylase in brain and peripheral tissues. Nerve stimulation is not associated with a shift in the subcellular distribution of this enzyme in chromaffin cells of the adrenal. While most of the enzyme appears to be located in the cytosol, a small fraction is associated with chromaffin granules. The proportion which is associated with granules does not increase during stress and adrenal secretion. This group has made the interesting finding that brain transplants in oculo and in situ manifest good viability and make functional connections with host brain or subsequent grafts. The development of appropriate histological and functional organization can be readily demonstrated. Chromaffin cells in oculo or in the lateral ventricle alter their morphology to a neuronal phenotype and can provide functional catecholamine input to host brain in the latter case.

Biochemistry and Pharmacology

Considering the need for better pharmacological tools to treat movement disorders such as Parkinsonism, Huntington's disease, Tourette's syndrome, and tardive syskinesia, the discovery of the clinical efficacy of apomorphine has aroused considerable interest. An investigator at the University of Texas is continuing a program of basic research on the metabolism of apomorphine (APO) and N-n-propylnorapomorphine (NPA). These two drugs have shown definite promise as clinically useful anti-Parkinsonian agents. His work has shown that apomorphine's clinical efficacy may be related to its dopaminergic activity. The investigators will continue their work developing analytical methods for studying these drugs and their analogs and in metabolites in biological material, and will pursue ways to overcome the deleterious side effects of the drugs, particularly azotemia.

A number of substances that are strong candidates for neurotransmitters in the mammalian CNS are found in high concentrations in the basal ganglia. These include acetylcholine (ACh), dopamine (DA), serotonin (5HT), gamma-aminobutyric acid (GABA), substance P and taurine. Little is known about the effect of these substances and other putative neurotransmitters on the responsiveness of neurons of the globus pallidus. Other researchers at Texas are studying the responsiveness of primate pallidal neurons to neurotransmitters. GABA, glycine, taurine and beta-alanine depressed the spontaneous firing of neurons located in all pallidal segments. GABA was the most powerful depressant and stopped spontaneous firing of many neurons with currents less than 5 nA. Cells located in the internal pallidal segment were generally more responsive to the depressant action of GABA than cells located in the external segment of laminar region. In general, glycine was not as effective a depressant as was GABA.

Work at the University of Michigan may provide a better clinical understanding of the spasticity associated with Parkinsonism as well as giving insight into the fundamental mechanisms underlying basic spinal cord neuropharmacology. Experiments will measure neurochemical changes and synaptic function within the spinal cords of rats and cats with spinal cord transections as the animals develop generalized spasticity. This laboratory has developed a technique for studying GABA turnover by high pressure liquid chromatography. Preliminary work show a 100% increase in GABA turnover in flaccid paraparesis compared to sex-matched, litter-mate, sham-operated controls.

Neurophysiology and Neuroanatomy

Scientists at the University of Washington are examining the neurons of the entopeduncular nucleus (ENT) and describing efferents to and afferents from this area, as well as the synaptic actions of ENT cells of several brainstem sites which may link the ENT to the globus pallidus. The investigators seek to clarify what drives the high tonic firing rate characteristic of pallidal and nigral basal ganglia output neurons in awake animals. This laboratory has shown that microstimulation of the globus pallidus with 100 uA pulses at 300 per second interfere with the performance of a monkey in a button-pushing task in a manner somewhat analogous to the bradykinesia syndrome. Lesions of the same area produced by injection of kainic acid also produced slowing of movement in this task. This group has also shown reciprocal connections between the globus pallidus and the pedunculopontive nucleus.

Investigators at the Johns Hopkins University are utilizing electrophysiological and anatomical methodology to explore the motor functions of the basal ganglia. In normal and lesioned monkeys, they are seeking to clarify further the normal functions of the basal ganglia in the regulation of movement and posture and to unravel the pathophysiologic mechanisms underlying movement disorders in man. Trained monkeys are given visuomotor tracking tasks while neurons in key brain areas are monitored as the monkeys perform a limb movement. This work comprises some of the best and most exciting single unit analyses of basal ganglia activity in awake monkeys.

They have shown that the activity of the majority of cells in the globus pallidus and subthalamic nuclei are modulated by movements of individual body parts. However, the majority of this cellular activity was related to arm and leg movements. In the pars reticulata of the substantia nigra, however, neuronal activity was rarely related to limb movements, but many discharged physically in relation to licking and chewing movements. Other studies indicate that the major determinant of neuronal discharge during a limb movement for basal ganglia (BC) neurons is the direction of movement. While changes in neural activity occur during the reaction time period, the majority of cells change their activity during the period before the onset of movement, but after the first change in EMG activity. These data thus suggest that the BG may not play a role in the initiation of limb movements, but rather in the control of ongoing limb movements. Moreover, their role may be more related to the selection or energizing of muscles than in the specification of movement parameters.

Huntington's Disease

Huntington's disease (HD), a fatal degenerative hereditary condition, is a disorder of the basal ganglia closely related to Parkinson's disease. While

Parkinsonism produces tremor and rigidity, Huntington's disease causes uncontrollable chorea, and gradual loss of the capacity to walk, talk, swallow, and maintain oneself independently. The majority of patients show some degree of dementia, beginning with loss of short-term memory and organizational skills and progressing to a severe incapacity toward the end of the illness. Profound emotional disturbances mimicking schizophrenia and manic depressive disorders may also occur. Huntington's disease is transmitted as an autosomal dominant gene and usually manifests itself between the ages of 35 and 45 years. Children comprise 10% of cases. Treatment is merely palliative and most often entails the administration of dopamine blockers or antagonists. There is no test to determine if a child of a Huntington's disease patient is carrying the lethal gene before symptoms of the illness appear. Patients generally live 10 to 20 years following symptom onset. Biochemically, the disease is characterized by reduced stores of GABA, glutamic acid decarboxylase (GAD), acetycholine (ACh), substance P, angiotensin II converting enzyme and variety of other neurotransmitters and neuromodulators. There is almost total loss of the small neurons of the caudate nucleus and putamen as well as cortical atrophy, giving rise to a typical picture of enlarged ventricles and sulci on CAT scans.

Genetic Studies

A number of investigators are continuing laboratory work to identify the abnormal gene that is responsible for the host of physical and mental symptomatology that characterizes Huntington's disease. In a disorder as relatively uncommon as Huntington's disease, and with family members so widely dispersed geographically, a centrally located data bank of pedigrees is an invaluable aid to research. A contract for a Huntington's Disease Roster was given to the University of Indiana to develop such a roster, in response to a recommendation of the Commision for the Control of Huntington's Disease and Its Consequences. The Roster can match together family members with different names and from disparate states, thus creating much larger pedigrees It can also select specific families needed for particular research projects and serve as an intermediary between the scientist and the subject.

Studies of Non-neural Tissues

An investigator at Duke University is pursuing his preliminary data which indicate alterations in cell attachment and protein glycosylation in HD fibroblasts. In particular, glutamine was found to be toxic to HD fibroblasts leading to changes in morphology and eventual cell death; these effects are partially reversed by glucosamine. On the basis of these and other observed abnormalities, the investigator suggests that HD fibroblasts express a membrane defect due to abnormal glycosylation of proteins and that this impaired glycoprotein synthesis may be correctable by a diffusible factor in serum. His work proposes to characterize these differences further, and to pursue the hypothesis that the enzyme responsible for glucosoamine synthesis, fructose-6-phospate glutamine transaminase, is the defective metabolic step in producing the disease. At this point the enzyme has been purified from fibroblasts 1300 fold. Preliminary analysis indicates that nutritional modulation of this enzyme by sugar and serum concentration are important biological variables in tissue culture.

Biochemical and Structural Studies

Animal models have always been important in the understanding of the etiology, pathogenesis, and possible treatment of disease. HD is no exception. Recently, a new animal model was created by the injection of kainic acid, a highly toxic glutamate analogue derived from seaweed, into the striatum of rats. The kainic acid produces a selective degeneration of striatal intrinsic neurons, and neurochemical and histologic alterations in the nigro-striatal circuit that closely mimic those found in HD. Fibers of passage are less affected by the kainate, and the chemical has no effect if cortical-striatal glutamatergic pathways are served.

An investigator at The Johns Hopkins University School of Medicine is continuing his work of elaborating the lesioning effects of kainic acid. In vitro measurements are being made of the specificity of receptor binding of kainic acid and kainic acid-induced release of labeled neurotransmitters from prelabled slices of hippocampus, striatum, and cerebellum. In vivo studies focus on the effects of kainic acid injections on local brain energy metabolism. Studies have been completed on the acute metabolic effects of kainic acid and related excitotoxins within the striatum; and considerable progress has been made in the characterization of excitatory acidic amino acid receptors using ligand-binding techniques. Recently, they have developed preliminary data for the existence of a presynaptic receptor for kainate on reputed glutamatergic neurons and of the existence of endogenous peptides that interact with a high degree of specificity and high affinity with the glutamate receptor.

Interdisciplinary Workshops

A crucial need in Huntington's disease research is to recruit new investigators to the study of this relatively little known disorder, and to generate new research hypotheses. The Hereditary Disease Foundation has had a ten year program of sponsoring interdisciplinary workshops on Huntington's disease and other degenerative disorders to achieve these ends. Participants range from postdoctoral and medical students to department chairmen and span a wide variety of scientific expertise in basic and clinical areas. Four workshops a year are being supported through a grant to the Foundation.

Huntington's Disease Center

One of the most exciting initiatives in Huntington's disease research was the award of two grants in FY80 to establish "Centers Without Walls", as recommended by the Congressionally mandated Commission for the Control of Huntington's Disease and Its Consequences. Each Center supports clincial and basic research aimed at uncovering the etiology and pathogenesis of Huntington's disease and developing new physiological and sociopsychological treatments for the disorder. One Center is located at The Johns Hopkins University and is composed of a number of different departments within the Medical School, such as psychiatry, neurology, genetics, and the School of Public Health. The program consists of nine clinical and basic research projects. Clinical studies range from case-finding and epidemiological studies, and research on genetic counseling, to the exploration of eye movements as clues to early disease process and diagnosis, and the amelioration of swallowing difficulties. Basic science projects include the localization and measurement of neurotransmitters,

neuropeptides, and enzymes in the brain, and the detailed elaboration of the structure and function of the basal ganglia, an area of the brain affected by Huntington's disease, Parkinson's disease, Tourette's syndrome and many other movement disorders. A survey of Huntington's disease in Maryland has been completed. Using the clinical and genealogical data collected from patients and persons-at-risk in the Maryland survey, a number of studies have been completed. These are: 1) the genetics of HD, 2) psychiatric research on affective disorder and at risk offspring, 3) neurology, 4) diagnosis and 5) neuropathology. An educational and counseling course has been established and a newsletter published.

The other "Center" represents a consortium of departments within different institutions, including Massachusetts General Hospital, McLean Hospital, Boston University, Tufts New England Medical School, the Boston Veterans Administration Hospital, and the University of Massachusetts, and supports 10 scientific investigations in participating institutions. Patients and their families are being seen at clinics in the different Centers. A total of 225 different individuals from 100 apparently unrelated HD families have been seen. The standard collection of information included the completion of 100 Family Histories containing a total of 3,699 individuals both living and dead. Age of onset has been specified for 211 of the 520 designated HD gene carriers in the stored families. The most striking finding is that in early onset 70% inherit the gene from an affected father, this reduces to 48.5% for mid-life onset and 20% for late-life onset. The sex of the affected parent has a profound influence on age of onset. Patients and their families are being seen at clinics in the different Centers. A number of the projects focus on mapping and measuring levels of neuroendocrines and neuropeptides. These investigators are developing new procedures for analyzing brain tissues which will be of value for looking at all brain disorders. In addition, they are examining tissues from patients dying of other devastating brain diseases such as schizophrenia, Alzheimer's disease, Parkinson's disease and others. Studies have been completed in a series of brain extracts from patients with Huntington's disease and compared with those of controls. Results have demonstrated definitively the preservation of neuronal elements containing somatostatin in the caudate and putamen as well as in the external and internal segments of the globus pallidus in patients with Huntington's disease. Studies have confirmed previous reports that the same areas of brain have diminished concentrations of substance P, indicating that the selective preservation of somatostatin is accompanied by reduction of another neuropeptide. A team of molecular geneticists at Massachusetts General Hospital is using recombinant DNA techniques to try to determine the exact chromosomal location of the abnormal Huntington's disease gene. These scientists are in the process of mapping the human genome, uncovering "markers" on chromosomes which will greatly advance the localization of other genetic diseases. They use tissue samples from families with special pedigrees, particularly from Venezuela. Arbitrarily chosen single copy DNA segments have been cloned and used as hybridization probes against restriction enzyme digested DNA from 6 or more unrelated individuals. A procedure has been established for isolating clones containing only single copy DNA.

Venezuela Project

A major project of the NDP Huntington's Disease Program has been the study of a unique population of Huntington's disease families living on the shores of Lake

Maracaibo. In July, 1980, a contract was signed with the University of Zulia, in Maracaibo, to enable a team of Venezuelan and U.S. scientists to study the families neurologically, genetically, psychologically and sociologically. The Venezuelan focus is particularly valuable for research purposes for the following reasons: 1) a single founder means that all patients have inherited an identical HD gene. 2) Families are extremely large with many members both affected and unaffected. 3) The families are interrelated, with a relatively high frequency of two people "at risk" for the disorder, marrying and producing children who have a higher probability of being homozygotic, if a "double dose" of the gene is not lethal in utero. 4) None of the patients are taking any medications so that drug effects do not confound the data.

Geneticists from the Boston "Center Without Walls" are analyzing the tissue collected using recombinant DNA techniques to identify DNA polymorphisms linked to the HD gene. Transformed lymphocyte lines and fibroblasts are available for any qualified investigator to use and may be obtained from the Institute of Medical Research, Camden, New Jersey. The Venezuelan pedigrees have been computerized and are part of the Huntington's Disease Roster at the University of Indiana. Preliminary analysis of the pedigrees obtained in the study of Huntington's patients in the Lake Maracaibo area has identified one individual in the remote fishing village of Lagunetas who may have inherited the Huntington's disease gene from both parents. If confirmed, this homozygosity, not known to have occurred previously, may aid in precise localization of the Huntington's disease gene on a specific chromosome.

Alzheimer's Disease and Other Dementias of Aging

The problem of the dementias in the United States has assumed alarming proportions. At least two-thirds of elderly people with advancing dementia suffer from Alzheimer's disease (AD). In recent years, many scientists have argued that distinctions between presenile dementia and Alzheimer's disease are arbitrary and meaningless.

The classical neuropathology of AD is characterized by abnormalities of the cerebral cortex. The three pathological hallmarks of the disease are: neuritic plaques consisting of abnormal neurites associated with extracellular amyloid; perikaryal neurofibrillary tangles comprised of accumulations of paired helical filaments; and granulovacuolar degeneration.

Structural Studies

The majority of the research supported is aimed at clarifying the structural and biochemical abnormalities which characterize Alzheimer's disease. A number of studies focus on cytoskeletal changes, the neurofibrillary tangles and senile plaques. These tangles appear in the neuronal soma as aggregates of paired helical filaments approximately 200 A in cross section, with a twist approximately 80 A along their length. Both neurofibrillary tangles and their normal, unpaired, and nonhelical neurofilamentary counterparts have been identified as proteins with a molecular weight of around 50,000 daltons. Several different laboratories are investigating paired helical filaments in the presenile and senile dementias as well as in Down's syndrome. Twisted tubules have been partially purified by investigators at New York University Medical Center. The relationships among various neurofilaments and between these

filaments and tubulin are being explored. Another investigator at Boston Biomedical Research Institute is characterizing the chemistry and function of neurofilament proteins with regard to their sequencing, immunoreactivity, comparability with other glial fibrillary proteins, and tendency to proliferate in neurons treated by neurolathyrogens. Neurofibrillary degeneration induced by spindle inhibitors and aluminum salts have been previously studied as a model of human neurofibrillary degeneration seen in senile dementia of Alzheimer type and other neurological disorders. Recent studies suggest that the formation of neurofibrillary tangles in neuronal perikarya is not caused by new synthesis of neurofilament proteins, but rather by retrograde transport and relocation of these proteins in the perikarya.

Recently, investigators have succeeded in labeling tubulin, brain microtubule accessory proteins (MAP) and clathrin with the fluorescent compound dichlorotriazinylamino fluorescein (DTAF). This work suggests a very high specificity of the MAPs and suggests that they may be controlling elements in determining the type of cytoskeletal array which is formed.

Researchers are immunochemically isolating and characterizing the Alzheimer neurofibrillary tangle (ANT), crossreacting antigens from normal young human and animal brains. They are studying the presence of normal neurofibrillary proteins and of serum proteins in ANT by immunocytochemical techniques, to identify ANT-crossreacting antigens in normal neurofibers, and to compare ANT with neurofibrillary tangles in other human conditions. Previously, they demonstrated the presence of an ANT-crossreacting antigen/s in normal young human and animal brains by immunocytochemical labelling of the tangles with an antiserum raised against an in vitro assembled microtubule preparation. In order to elucidate the question if normal neurofibrillary proteins are an integral part of the ANT, they studied the reactivity of ANT with antisera against different neurofibrillary proteins using the peroxidase anti-peroxidase technique. The findings suggest that paired helical filaments might contain more than one antigen. It appears that the ANT-crossreacting antigens present in normal brain are different from the known microtubule or neurofilament polypeptides.

Recent studies by NINCDS grantees strongly suggest that the neurons in the nucleus basalis of Meynert (nbM) selectively degenerate in AD. On the basis of these observations, it has been hypothesized that a selective lesion in the nbM is, in substantial part, responsible for the cholinergic abnormalities in the cortex.

Biochemical Studies

Other research sponsored by the Institute is aimed at characterizing the biochemical alterations in SDAT. The acetylcholine muscarinic receptors of the cortex are maintained even though there may be a 75% to 95% loss of cortical choline acetyltransferase (ChAT). Localization of this synthetic enzyme and its receptor is being pursued in human and animal brain tissue by enzyme immunohistochemistry and radiography. Microscopic, histologic and biochemical techniques will be used to compare young and old brains and normal and senile dementia of the Alzheimer's disease type brains.

Investigators have shown a close correlation between in vivo synthesis of acetylcholine (ACh), glucose oxidation, and behavior during hypoxia; similar

effects of hypoxia on ACh synthesis and glucose oxidation could be demonstrated with brain slices or isolated synaptosomes making it likely that the observed in vivo effects on ACh synthesis were not a secondary effect mediated by other neurotransmitters. There is evidence for impaired Ca-dependent release of ACh from the nerve ending under hypoxic conditions, and this is thought to provide a feedback inhibition on ACh synthesis.

Animal models of dementia are hard to come by since dementia involves the loss of a capacity we cannot be sure animals ever had. Mutant mice can be excellent systems for studying degenerative processes. An investigator at Indiana University is studying the Purkinje cell degeneration (PCD) mutant as a model of selective cell loss in the nervous system. One model of both normal and pathological aging holds that there is genetically programmed cell death which gives rise to the characteristic signs of aging. In the PCD mutant, all Purkinje cells irreversibly degenerate. Preliminary work by the investigator on tissue culture explants of PCD cerebellum indicate that degeneration occurs at postnatal day 17. The laboratory has performed a quantitative analysis of the molecular layer of the Purkinje cell degeneration (PCD) mutant mouse. The results have shown that between control and 6 month old affected PCD's, there is a significant difference in number of parallel fibers. The parallel fibers in 6 month old affected mice are 57% of the control. Further loss occurs in the 9 and 12 month old animals. At 12 months of age, the parallel fibers in the strip of molecular layer are reduced to 17% of the control. The selective degeneration of a particular cell type allows the researcher to look at neurotransmitter functioning in the cerebellum, focusing on GABA which is a primary neurotransmitter for Purkinje, Basket, and Golgi cells. They have completed studies of the effect of the Purkinje cell loss on the noradrenergic system. The purpose of such study was to determine whether the loss of the Purkinje cell affects the amounts of norepinephrine or cyclic AMP in the cerebellum of mice between 25 and 280 days of age. No changes in norepinephrine content were detected during or after the Purkinje cell degeneration.

Clinical Studies

A large program project on "Senile Dementia: Alzheimer and Vascular Disorders" at Albert Einstein College of Medicine takes an interdisciplinary approach to studying the dementias. Clinicians, biochemists, neuropathologists and neurophysiologists, psychologists, mathematicians and many others turn their talents toward discovering the origin of these diseases and developing appropriate treatments. Investigators are interested in the nature, incidence, prevalence and course of senile dementias. The identification of risk factors and prevention will receive considerable attention.

The program has three major sections. Section I consists of laboratory studies relating to the etiology and pathogenesis of senile dementia, particularly of the Alzheimer type (SDAT). One project will attempt to grow paired helical filaments in culture. Another explores the possibility that a persistent virus infection may cause SDAT. Two other projects will focus on the localization (through immunocytochemistry) and regional distribution of five peptides in normal and senile human brains and explore the possible relationships of these peptides to the composition of neuritic plaques and tangles. They have observed reductions in somatostatin like immunoreactivity (SLI) and showed direct correlations to CHAT in AD and SDAT. They found that neurofibrillary tangles share common

immunological properties with elements present in normal brain and have developed new neuropsychological studies.

Section II continues several clinical and psychological studies of SDAT now in progress. A longitudinal study of 500 residents of a nursing home has generated a wealth of biological and psychological data. As residents die, approximately 40 brains a year are available for correlations of postmortem biochemistry with premortem clinical parameters.

The third section consists of a large prospective study of about 400 people drawn from two nursing facilities and "normal" elderly volunteers drawn from the community. The prospective study will identify risk factors in dementia produced primarily by multiple cerebrovascular infarcts. They have recently found a high incidence of ventricular arrythmia and bradycardia but a lower incidence of high density lipoproteins than in another large study.

New Directions

The NINCDS is actively seeking to increase the level of research effort directed at Alzheimer's disease and other diseases of aging. In concert with the National Institute of Aging, a Program Announcement was released soliciting grant applications on research into the etiology, pathogenesis, treatment and prevention of these devastating disorders.

General Studies

The primary neuronal cell type in the striatum is the striatal spiny efferent neuron (SENS). It receives presumed monosynaptic input from both cortex and thalamus and is reciprocally connected with the substantia nigra. Stimulation of various striatal afferent systems produces different synaptic actions on SENS. An investigator at Michigan State University is attempting to explain these different actions by morphological studies of synaptic inputs which he will correlate with physiological studies of these same afferents to intracellularly labeled striatal spiny neurons. A major thrust of this work has been the analysis of postsynaptic potentials evoked in neostriatal spiny neurons by stimulation in substantia nigra. This complex postsynaptic potential, which has both excitatory and inhibitory components, has been the subject of considerable study and controversy since it was first described by Hull and his associates in 1973. This laboratory's analysis has demonstrated this potential results primarily from inadvertent stimulation of axons in the vicinity of substantia nigra, rather than from substantia nigra neurons and their processes. The earliest excitatory component has been shown to be a monosynaptic axon reflex of collaterals from rapidly conducting brainstem-projecting neurons of neocortex. This was the first demonstration of the postsynaptic action of intrastriatal axon collaterals of pyramidal tract neurons by thalamic or cortical stimulation. This group has recently demonstrated that the underlying mechanism is disfacilitation of striatal neurons, rather than intrinsic inhibition as previously believed.

The demyelinating and sclerosing disorders grant portfolio includes research relevant to Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and the Ataxias. As of May 1982 there are 96 active grants, including 5 MS, 1 ALS, and 2 ALS-MS research program project centers. Total funding of this research is approximately $14.2 million from FY 1981 and 1982 funds. In FY 1982 a total of 104 applications were received and 83 were approved, of which approximately 13 new and 15 competing renewals were funded at a total cost of approximately $1.2 million for new research grants and approximately $1.9 million for competing renewal grants.

Multiple Sclerosis

As of May 1982, there are 37 active grants in the Multiple Sclerosis (MS) subprogram, including 5 MS and 2 ALS-MS research program project "centers". Total funding in support of these activities is approximately $9.1 million from FY 1981 and 1982 funds. A total of 45 applications were received, and 35 were approved of which 5 new and 4 competing renewals were funded for a total cost of approximately $700 thousand for new research grants and approximately $800 thousand for competing renewal grants.

1. Etiology and Pathogenesis

The most promising and active research efforts currently are directed toward putative immunological and/or viral etiologies and/or pathogenesis of MS. There is, for example, accumulating evidence that perturbations of T-lymphocyte function, particularly alterations of suppressor T-cell activity,occurs in MS patients. A recent finding is a decrease in T-suppressor (Ts) lymphocytes and an alteration in the ratio of T-helper (TH) to Ts cells preceding and during an acute attack of MS. It is expected that new research thrusts may further elucidate the role of the immune system in modulation or expression of neurological disease.

Studies are currently underway to: 1) investigate factors which cause genetically susceptible individuals to develop MS, 2) detect changes in immunological responses in relation to clinical changes, 3) determine immunologic responses to viruses, particularly myxoviruses, and 4) compare survival, rate of progression and disability among patients in high and low prevalence areas.

2. Immunology, Virology, and Research Models

Animal models of virus-induced demyelination are used to investigate the morphological and immunopathological features of myelin injury. Theiler's virus encephalomyelitis is one such model which is characterized by viral persistence in central nervous system (CNS) tissue. Studies demonstrate that demyelination in this model is probably immune-mediated.

The possibility that MS may be due to a dysimmune state continues to be a prime consideration in the pathogenesis of the disease. A good parallel may be drawn between MS and animal models of experimental allergic encephalomyelitis (EAE), in particular, chronic relapsing EAE. EAE can be produced in a variety of different species of animal hosts. Following injection of whole CNS tissue (or some of its

components, especially myelin basic protein) combined with an appropriate immunopotentiating agent, the sensitized host elaborates inflammatory immunologic responses leading to demyelination.

Acute MS is characterized in part by a perivascular inflammatory reaction which may simulate the inflamatory lesions of acute EAE. A main distinctive feature of MS is the extensive injury to the myelin sheath (and axons to a lesser degree) which results in large, grossly evident, plaques of demyelination. Chronic relapsing EAE resembles this characteristic MS feature rather closely.

Investigators at Northwestern University studing immune regulatory mechanisms in EAE in Lewis rats have found that splenocytes collected from rats sensitized to myelin basic protein together with complete Freund's adjuvant (CFA), cultured with concanavalin-A and later in MBP, enhance their EAE transfer capacity to syngeneic recipients. Some splenocyte preparations after more intense sensitization held little or no EAE transfer activity following culturing. They believe that this occurs because these splenocytes contain large numbers of monocytes (macrophages) with very potent suppressor activity. Removal of these macrophages allows the remaining splenocytes to be fully activated in vitro with concanavalin-A or MBP and to exhibit strong EAE transfer activity.

They found also that daily treatment of rats per os with indomethacin, from the seventh through the twelfth day after sensitization to spinal cord-CFA, resulted in a marked potentiation in the severity of EAE. It can be seen that with some further sophistication this system can be very useful in transferring EAE among allogenic rats and hamsters. The explanation of these observations would appear to lie in rapid proliferation of monocytes (probably macrophages).

EAE supernate transfer activity, released from briefly cultured lymph node cells of a donor sensitized to spinal cord-CFA, but not MBP-CFA, elicits the typical histopathologic changes of EAE in recipient rats but is never accompanied by clinical signs of the disease. This is under study in the laboratory, and the goal is to define in biochemical terms the "transfer" factor and to identify its specific function.

Some oligoclonal bands in the CSF of patients with MS and subacute sclerosing panencephalitis appear to contain antibodies which react with both measles virus and myelin basic protein. Because of the serological and epidemiological evidence linking measles virus to MS, evidence for persistence of the virus genome in MS tissue is sought. Very recent efforts have succeeded in identifying measles virus genome in brain tissue of two of six cases of MS using new, highly sophisticated hybridization techniques.

3. Selected Examples of Research Activities

Since proteolipid protein (PLP) was discovered, very little information has accumulated about it because of its insolubility in aqueous solvents and its high degree of association with lipids. Attempts to isolate PLP usually leads to aggregation and denaturation. An investigator at Washington University in St. Louis overcame many of these difficulties and is making progress toward PLP characterization.

This antiserum can be also used in other animals indicating a lack of species specificity of proteolipid protein. Antiserum to PLP from various animals does not demyelinate spinal cord cultures nor cause inhibition of myelin synthesis in culture. However, antisera to PLP from animals injected with galactocerebroside, or CNS myelin, does demyelinate cultures.

Although MBP and PLP proteins are present in oligodendrocytes, neither protein was observed in oligodendrocytes until substantial differentiation of these cells had occurred, and oligodendrocytes were positive for MBP before PLP was visible. These studies indicate that the MBP is added to the myelin prior to PLP, and there is a shift in priority of synthesis from MBP to PLP in individual oligodendrocytes during the process of myelination. Moreover, very small fibers contain low concentrations of MBP relative to PLP, and conversely, very large fibers contain a high concentration of MBP relative to PLP. Thus, the relative concentration of these proteins in myelin is not constant but varies as a function of the size of the myelinated fiber.

An investigator at Johns Hopkins University in Baltimore, Maryland, studies proteins and glycoproteins found in oligodendroglial plasma membranes in a cell culture system. Oligodendroglia can be purified by bulk-isolation techniques from bovine, lamb, or human subcortical white matter tissue. The preparation is up to 95% homogeneous. Purified oligodendroglia can be maintained as suspension cultures for several days, and some cells can be maintained for several weeks. The maintained cells are viable as indicated by the rapid incorporation of radiolabeled precursors into specific product. These cells synthesize lipids and proteins, especially lipids found enriched in myelin. After a short time in culture the oligodendroglia elaborate whorls of myelin lamellae, having the characteristics of mature compacted myelin.

An investigator at the Temple University in Philadelphia analyzes the biochemical aspects of myelination. He has shown that thyroid hormone (T3) stimulates oligodendrocyte to produce myelin.

The MS center at the Albert Einstein College of Medicine in New York City has demonstrated that non-IgG immunoglobulins as well as IgG mediate complement-dependent demyelination in CNS cultures, immunoglobin-binding to myelin and oligodendrocytes, and IgG caused myelin swelling and oligodendrocyte proliferation. Parallel investigations of serum from MS patients have demonstrated that some factors other than immunoglobulins may be the demyelinating factors. The work with sera from MS patients indicate that, unlike acute EAE, in chronic progressive multiple sclerosis patients most of serum demyelinating activity is due to complement-dependent non-immunoglobulin factors and that serum immunoglobulins play at most a minor role in the in vitro demyelination. It appears that the demyelinating factors in EAE sera are immunoglobulins and the demyelinating factors in MS sera may be enzymes.

Investigators at Duke University at Durham, North Carolina, have found extensive cross-species interactions of myelin basic protein that suggest that the antibody response is restricted to specific portions of the molecule which have been carefully preserved during evolution. They suggest that failure of antibodies to myelin components to affect myelinogenesis might relate to neutralizing serum factors; if sufficient antibodies are given, a positive effect may be achieved.

At the MS center at the Veterans Administration Medical Center associated with the University of California in San Francisco, a research team studies immunological activity of oligoclonal immunoglobulins in CSF, in extracts from nervous tissues of animals developing EAE, and in patients with multiple sclerosis using a relatively new technique called imprint electroimmunofixation. Using imprint electroimmunofixation they have found that approximately 50 percent of MS patients have CSF antibodies to MBP and measles confined to the oligoclonal region.

Studies have also been carried out in rabbits sensitized with MBP and complete Freund's adjuvant. Rabbits with herpes simplex encephalitis developed bands in CSF specific for herpes antigen. These findings are helpful in elucidating whether viral infection, or an autoimmune reaction, can reactivate latent clones of antibody-forming cells in the CNS, and produce an oligoclonal pattern as seen in MS.

The MS-ALS Center at La Jolla, California, is involved in studies of the cause and pathogenesis of demyelinating and degenerative disorders of the CNS. They have provided evidence that antibody can initiate and maintain virus persistence in vitro and that an antibody signal to a viral determinant expressed on the surface of infected cells can initiate unique changes in the cytoplasm of such cells. For example, the antibody to measles virus can strip viral antigens from the surface of infected cells and render these cells resistant to lysis by cytotoxic lymphocytes or antiviral antibody and complement. Further, experiments are in progress to establish whether the defect in the measles virus polypeptides, in antibody initiated virus persistence, is at the level of viral transcription or translation.

An investigator at the Medical University of South Carolina in Charleston, South Carolina, previously reported that MS patients suffering from active MS often exhibit high response to pokeweed mitogen driven IgG production, a T-cell dependent process. In contrast, new data show that MS patients' responses to the T-independent B-cell activator (salmonella paratyphi) are lower than observed in normal individuals. These preliminary findings indicate an abnormally low response to T-independent antigens which might be determined by a gene associated with the Ig structural gene.

The results obtained so far indicate that the changes in T-cell subsets in MS are actually related to simultaneous modifications of regulatory properties with regard to IgG production. This may be relevant to the disease process since an increase in intrathecal IgG synthesis during exacerbations has been reported.

An investigator at Washington University, in St. Louis, has shown an anomaly of multiple sclerosis T-cells when allogeneic T-cells and B-cells were co-cultured. Allogeneic normal T-cells and B-cells from HLA mismatched subjects and cultures of normal T-cells and multiple sclerosis B-cells generated about the same percentage of plasma cells. In contrast, allogeneic combinations of multiple sclerosis T-cells and normal B-cells generated a several-fold-increased percentage of plasma cells. This data supports the theory that T-cell lymphocytes from patients with active MS are deficient in a subset of cells that negatively modulate allogeneic B-cell activation. The deficient subset could conceivably be a suppressor or cytotoxic cell. Suppressor cytotoxic T-cells are

radiosensitive and helper T-cells are radio-resistant. The investigator has found that irradiating normal T-cells increased the percentage of generated plasma cells much higher than irradiating MS T-cells. This data supports the recent report that patients with active MS have a diminution of suppressor cytotoxic T-cells called OKT5.

4. Laboratory Assessment

No definitive diagnostic laboratory tests for MS are known. Progress has been made in the early diagnosis of MS utilizing visual, auditory, and sensory evoked responses and computerized tomography. Clinically unsuspect lesions may be identified by these and other new methods.

The oligoclonal immunoglobulin assay is helpful in confirming the diagnosis of MS in 90-95% of the cases. A highly sensitive radioimmunoassay is being used to assess demyelination and myelination using nucleotide rich material (NRM) found in the CSF which is unique to MS patients. Further, an attempt is being made to verify the presence of neuroelectric blocking factor(s) reportedly found in serum obtained from patients with MS.

A group at Johns Hopkins University, and others, have reported that basic protein appears in the cerebrospinal fluid (CSF) of MS patients undergoing an acute attack. The presence of myelin basic protein in the CSF of MS patients undergoing acute attacks may have practical significance in assisting in the early diagnosis of MS and permitting monitoring of the activity of the disease in patients with confirmed MS. Myelin basic protein assay in CSF may also prove to be a useful tool for measuring response to therapy.

5. Treatment and Clinical Trials

There is no wholly safe and effective treatment for MS. ACTH and steroids continue to be used in tne treatment of exacerbations of MS. Clinical trials are exploring immunosuppressive therapy with azathioprine, prednisone with azathioprine, and cyclophosphamide in chronic progressive MS. A study of the efficacy of co-polymer I on recent bouts of MS at the Albert Einstein College of Medicine is showing promising results. A multicentered collaborative study of plasmapheresis in the treatment of exacerbating-remitting MS is underway.

6. Summary and Future Trends

The application of new techniques has resulted in the identification of two different viruses in MS brain tissues but these observations remain to be confirmed. In addition, blood and spinal fluid of MS patients have antibodies to a variety of viruses. Studies are continuing in an effort to uncover the possible relationship of infectious agents to MS. Research on mechanisms of persistence of viruses in tissues has been ongoing and although a number of mechanisms have been identified, others remain to be confirmed. The NINCDS continues to support studies defining the immunological abnormalities of MS patients and the causes and mechanisms for their development. The most important results thus far relate to a significant reduction of cells whose function is to suppress immunological reactions prior to and during acute attacks of MS. The most intensive research currently is in the immunological area. Progress has been made in improving the reliability of diagnosis in MS. Clinical trials are

supported by NINCDS and by other agencies here and abroad. Genetic studies have uncovered an association between MS and patterns of histocompatibility antigens. Factors which may have an influence upon the course of MS are being studied. Recently, evidence has been uncovered which suggests that location and/or frequency of change in the patient's residence may be important in the development and course of MS. Techniques for growing oligodendroglial cells (which form and maintain myelin) in tissue cultures have been developed and a variety of studies are in progress using this system.

Amyotrophic Lateral Sclerosis

The human motor neuron disorders (MND), of which amyotrophic lateral sclerosis (ALS) is one, are a group of neurological disorders characterized by weakness, muscle atrophy, and widespread denervation. There is evidence that the MND's represent a spectrum of diseases with common clinical and pathological features. Genetic studies suggest a variety of modes of inheritance: autosomal recessive, dominant, and polygenic. The infantile spinal muscular atrophies are inherited as an autosomal recessive trait, and some of the familial cases of ALS appear to be inherited as an autosomal dominant. In many other families the mode of inheritance is less well defined. Most of the cases, however, are sporadic.

As of May 1982 the Amyotrophic Lateral Sclerosis (ALS) subprogram had 11 active grants which included one ALS research program project center. The total cost expenditure from FY 1981 and 1982 funds for these research activities is approximately $1 million. This includes 1 ALS "center". When the additional two ALS - MS "centers" are also included, the number of active grants is 13 for a total cost of approximately $2.9 million. In FY 1982 19 applications were received, and 15 were approved, of which 2 new and 4 competing renewals were funded at a cost of approximately $90 thousand for the new and approximately $0.5 million for the competing renewal grants. In FY 1980 the Neurological Disorders Program issued a Program Announcement (PA) calling for grants on the Motor Neuron Diseases, Spinocerebellar and System Degenerations. The response to this PA, which also embraced grants on ataxias, has been modest.

1. Etiology and Pathogenesis

The etiology of the motor neuron diseases remains unknown. One theory holds that ALS is due to accelerated aging of the motor neuron, which is genetically programmed. ALS has been thought to be associated with secondary factors such as prior poliomyelitis, neoplasia, or excessive athletics. That ALS is due to multiple etiological factors is supported by the following: familial cases can be either autosomal recessive or dominant; genetic and environmental interaction is seen in familial and nonfamilial clusters in Guam; and dizygotic male twins developed ALS in the sixth decade. There is some variability both in the duration of illness and in the pathology of the familial forms of the illness. Variations are also noted in the sporadic form of ALS where 20% of afflicted are alive after five years. ALS has been reported in association with dementia and degeneration of other systems.

2. Virology, Immunology, and Animal Models

Attempts to transmit MND to chimpanzees (Gibbs and Gadjusek) by the inoculation of brain and spinal cord tissue from patients with ALS have so far been

negative. Despite the expectation of uncovering a latent or persistent virus infection in ALS, the search for the presence of virus has been unrewarding. There are only vague suggestions of immune dysfunction in ALS, which require additional study.

Animal models are important in the study of MND. Several have been identified and are being studied intensively including an hereditary canine spinal musclar atrophy (HCSMA) of Brittany Spaniels which was found by investigators at Johns Hopkins. Other models include Wobbler mouse, Swedish Lapland dogs, Stockard's paralysis in large dogs, and murine retrovirus poliomyelopathy. Toxic models are also being investigated.

3. Selected Examples of Research Activities

At the ALS center at St. Vincent's Hospital in New York City, a research team is actively engaged in studies of several aspects of ALS etiology and the pathogenesis of ALS. Their study of the distribution of HLA-A, -B, and -C in patients with ALS found no statistically significant deviation. They found a trend, however, toward a decrease in HLA-A9, and toward an increase in HLA-Bw35 and -Cw4.

In the past year, by employing modern analytical equipment, scientists at the center detected abnormal levels in ALS brains of CNS gangliosides, and their ratios to each other, perhaps due to defective synthetic pathways. These findings, when confirmed, could become a part of a diagnostic battery for ALS and may help in establishing the etiology of ALS.

An investigator at the University of Southern California, at Los Angeles, is studying the effects of neural differentiation on viral replication, differencesin viral replication in the neural, glial, and non-neural cells, effects of cell division on viral replication, and the effect of viral clonal variation on viral replication in the neural or glial cells.

Theiler's murine encephalomyelitis virus related to human poliomyelitis, has a particular affinity for motor neurons and causes neuro-degenerative disease in mice.

Using this model, these scientists have found that cellular differentiation and the arrest of cell division can alter Theiler's virus replication. The preferential replication of Theiler's virus in dividing cells in vitro, as well as in neurons, reflects age and cellular specific changes.

4. Treatment

At present, there is no effective treatment for ALS. Symptomatic relief of excessive salivation may be achieved pharmacologically. Past treatments which have proven ineffective include neurotoxin, corticosteroids, immunosuppression, immunostimulation, transfer factor, and plasmapheresis. No clinical trials in ALS are presently supported by the Institute.

5. Summary and Future Trends

Motor neuron diseases constitute a host of disorders about which little is known. New ideas and research initiatives are needed which will lead to a better understanding of these disorders and thus to effective management, treatment, and prevention.

The Program has stimulated research interest in ALS by issuing a program announcement in May, 1980. Grantees supported by NINCDS are continuing the search for possible viral causes of the disease utilizing the most sophisticated techniques. The search for nutritional and metabolic abnormalities in ALS continues. The Intramural Program has identified a condition resembling poliomyelitis, which occurs in families in which ALS occurs. The possible cause of this illness and its relationship to ALS is being explored. A dog model for ALS has been identified and studies of its pathology, clinical course and genetics are progressing. Unsuccessful therapeutic trials for ALS utilizing various modalities have been conducted.

Future trends in ALS and related research are expected to concentrate on animal models, axonal transport, and toxic neuropathies, and the possible effects of target organs on motor neurons.

Ataxia

As of May 1982, the Ataxia subprogram had 5 active grants. The total cost from FY 1981 and 1982 funds for these research activities is approximately $300 thousand. In FY 1982, 6 applications were received and 2 were approved. Two new grants were awarded at a cost of over $100 thousand. No awards were issued for the competing renewal grants. In the FY 1980, the Neurological Disorders Progam issued a Program Announcement calling for grants on Motor Neuron Diseases, Spinocerebellar and System Degenerations; that is, ataxias and motor neuron diseases.

Estimates of people afflicted with ataxia range from 5,000 up to 20,000, in the United States. The ataxias include a variety of disorders, primarily heredofamilial, currently classified on the basis of clinical and pathological features. Although ataxia may be a part of the clinical picture of a whole host of disorders, the primary interest of this subprogram is in those in which uncoordinated movement, due to involvement of the cerebellum and/or its pathways, is a principle feature.

1. Etiology and Pathogenesis

The symptoms of ataxia may begin during childhood, adolescence, young or mid-adulthood, depending upon the disorder. The causes of cerebellar ataxia include developmental defects, such as cerebellar agenesis and hypoplasia, progressive degenerative disorders, such as familial spino-cerebellar degeneration, Friedreich's ataxia (most common form), and ataxia telangiectasia.

Friedreich's ataxia is a progressive degenerative disorder affecting the nervous system, heart, and certain enzyme systems. An abnormality of pyruvate decarboxylation was observed in some patients, but still needs further confirmation. Recent data suggests a reduction of activity of mitochondrial

malic enzyme, an enzyme involved in regulation of carbohydrate metabolism. In general, however, we must state that no specific biochemical defect has been found in the majority of the patients with clinically and pathologically defined hereditary ataxias such as cerebello-olivary ataxia, olivo-ponto-cerebellar atrophies (OPCA), and spastic ataxia.

2. Research Models

An investigator at Johns Hopkins University in Baltimore, Maryland, is studying canine inherited ataxia in the Gordon setter dog. The pathological changes, especially in older dogs, resemble those of the familial human cerebellar cortical atrophies. There are significant clinical and histological similarities, as well as some pathological differences, between the animal and human ataxias. Clinical, morphological and genetic studies, currently in progress, will hopefully demonstrate the significance of this potentially valuable animal model.

3. Selected Examples of Research Activities

An investigator at Mount Sinai School of Medicine in New York City found that patients with adult-onset olivopontocerebellar atrophy (OPCA) that was either sporadic, or genetic recessive, had a significant reduction in leukocyte glutamate dehydrogenase (GDH) activity. The defect was found to be specific for this form of OPCA since patients with the dominant form of OPCA as well as other types of spinocerebellar degeneration were found to have normal enzymatic activity in leukocytes.

An investigator at University of Mississippi Medical Center at Jackson, Mississippi, attempts to determine the genetic linkage relationships of autosomally dominant inherited spinocerebellar ataxia. A determination of antigens at the HLA A and B loci within the histocompatibility complex on human chromosome 6 have formed the major basis for the linkage studies. Additional genetic markers thought to be located on human chromosome 6 near the HLA complex are currently the subject of additional investigation.

4. Summary and Future Trends

The ataxias, like motor neuron diseases, constitute a heterogeneous group of disorders about which relatively little is known. New ideas and research initiatives are needed. Of the current research efforts, measurements of selected enzyme activities and study of animal models appear to be the most promising.

INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

The Infectious Diseases subprogram supports investigations of viral, bacterial, and parasitic infections, and research on any infectious agent that might be suspected to be the cause of a degenerative disease of the nervous system.

In fiscal year (FY) of 1982, 31 grants were active in the infectious diseases subprogram. This includes two program project centers. Total costs from FY 1981 and 1982 funds for these research activities is approximately $3.5 million. In FY 1982 a total of 19 applications were received and 17 were approved, of which 3

new and 5 competing renewals were funded at a total cost of approximately $450 thousand for new research grants and approximately $500 thousand for competing renewal grants.

It is suspected that many neurological diseases or disorders are caused by viruses, although a particular virus has not been identified. These include: Reye's syndrome, Guillain-Barre syndrome, multiple sclerosis, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, some forms of Parkinson's disease, and congenital defects.

The programmatic aims of this subproject are: 1) to determine the etiology of degenerative diseases of the nervous system of man by experimental transmission of diseases to animals; 2) to develop animal models for characterization of the isolated etiological agents of these diseases; 3) to uncover therapeutic regimens for the prevention and/or control of these diseases in animals and to determine their safety and efficacy for use in man: 4) to study viral, bacterial and parasitic diseases of the nervous system; 5) to provide support for research activities relevant to MS, ALS, and other neurodegenerative diseases; 6) to provide support for research relevant to the dementia subprogram.

1. Creutzfeldt-Jakob disease

Clustering of cases of Creutzfeldt-Jakob disease (CJD) has not been found in the U.S.although it does occur in other countries. About 15% of the cases are of the familial type which may suggest a genetic susceptibility to infection. It remains to be determined whether the agent of CJD is maintained only by patient to patient transmission, is shared by man with lower vertebrates, or whether it is a latent infection of man that is rarely activated. The CJD agent may turn out to be very similar to the scrapie agent, which is believed to be a very small molecule of genetic material.

An investigator at Yale University in New Haven, Connecticut, studies the pathogenesis of experimental Creutzfeldt-Jakob disease in guinea pigs, hamsters and mice. Light and electron microscopic (EM), virological, tissue culture and biochemical techniques are utilized. The leading hypothesis is that the CJD agent is composed of various viral strains with distinct incubation periods, or that it is a variant of scrapie.

2. Scrapie

Research is directed toward understanding the nature of the scrapie agent which affects sheep. Because the present assay for scrapie requires determination of an endpoint by titration in mice over a nine-month period, it is especially tedious to purify the scrapie agent and use this preparation to study its chemical and immunological properties.

An investigator at the University of Wisconsin in Madison, Wisconsin, was unable to adapt scrapie to grow in cell cultures, but has found that inhibiting cell growth allowed cultured virus to maintain infectivity for longer periods in vitro. Recent results suggest that scrapie is caused by a small naked virus bound to a protein molecule. Another investigator at the University of California in San Francisco reported recently that the scrapie agent is a protein molecule without a nucleic acid, or so small that it is not detectable.

3. Herpes Viruses

The importance of HSV-neural interaction lies in the critical role of infection in determining latency and reactivation in recurrent HSV-1 (cold sores, keratitis), HSV-2 (genital herpes) disease, as well as in the encephalitides caused by these viruses in both the adult (HSV-1) and neonate (HSV-2).

An investigator at the University of Utah School of Medicine studies the role of macrophages in CNS demyelination of athymic mice after corneal HSV infections. Previous studies have shown that after infection the immune competent animals had more extensive demyelination that the athymic mice. Recent studies show that as more cells respond to the lesion in the immune competent animals, the demyelinative lesions become more extensive. Electron microscopy demonstrates that macrophages may have a role in the demyelination. After infectious virus disappears from the chronically infected animals the mouse can remyelinate CNS axons with Schwann cells. Since the virus is usually confined to the trigeminal nerve and tract, and does not spread to other parts of the brain, studies are underway to elucidate this phenomenon.

An investigator at the University of Minnesota is also studying Herpes simplex virus infections of the nervous system. He has largely defined the progression of the infection as it moves from a peripheral site of infection through the peripheral nerves, via nerves into the spinal cord, and finally to the brain. This progression can be stopped in the nerves where the virus can establish a latent infection.

4. Marek's Disease Virus

An investigator at the University of Georgia, in Athens, studies genetic and immune mechanisms underlying the susceptibility of chickens inoculated with Marek's disease virus (MDV) to the development of transient paralysis. They try to determine which factors are responsible for the appearance of B blood group histocompatibility complex restriction of clinical transient paralysis to line G-B2 chickens. Previous findings indicate that the susceptibility to transient paralysis is controlled by a major histocompatibility complex.

To explore the immunological basis of transient paralysis (TP) caused by Marek's disease virus, the investigators suppressed B-cells by cyclophosphamide. Genetically susceptible chicks were given cyclophosphamide for four consecutive days after hatching. None of the cyclophosphamide-treated birds developed transient paralysis after infection with the Marek's disease virus while seven of the twelve cyclophosphamide untreated birds displayed symptoms of the disorder after the virus infection.

Since cyclophosphamide treatment has been found to transiently diminish T-cell dependent immunity, he performed a similar experiment with surgically bursectomized birds. None of the bursectomized birds developed transient paralysis after viral infection while seven out of nine control birds were affected. These results suggest the possibility that transient paralysis might be antibody-mediated. On the other hand, removal of the bursa, which is one of the sites of viral replication, might have lowered the virus load and consequently prevented expression of symptoms.

Results of the neurologic and electrophysiologic examinations that have been performed indicate that MDV-induced TP in chickens may provide a useful model for studying certain virus-caused central nervous system disorders that occur in man and other species. The finding that suppression of the humoral immune system prevents TP suggests that this disease may be an immune-complex or autoimmune type of disorder. This is an important finding which should by further studies lead to a better understanding of the mechanism responsible for the transient nature of this disease. The results which show that only certain strains of MDV will cause TP in chickens having certain genotypes indicate that there may be an essential, and perhaps complex, virus-host cell interrelationship for manifestation of disease symptoms.

5. Measles

One of the basic mechanisms by which viruses persist is the generation of defective interfering virus. In order to define the morphologic biology and pathogenetic mechanisms associated with defective interfering virus infection, a study of the natural or experimentally induced lymphocytic choriomeningitis virus infection in its natural host in the mouse is conducted.

An investigator at the University of Connecticut Health Center, in Farmington, Connecticut, studies the phenomenon of lymphocytes properties to adherence to virus infected cells. The investigator observed that blood lymphocytes attach to measles virus infected cells. Peripheral blood lymphocytes from MS patients adhere to measles infected cells in significantly increased numbers than control cells. The increased adherence of cells from MS patients appears to be due to a prostaglandin mediated event. This event is sensitive to inhibition by aspirin, and it is monocyte-dependent.

6. Demyelinating Viruses: Canine Distemper Virus and Visna

Canine distemper virus (CDV) causes persistent, demyelinating disease in dogs. By studying interferon levels in the serum of dogs, after infection with different CDV strains, it may be possible to differentiate between infection with an attentuated (no interferon) versus virulent (injected with interferon) CDV. It is known that interferon is present in the CSF of dogs with persistent brain infection. As of now, however, it is not known whether this phenomenon represents a cause or is a result of persistent infection.

A research team at the Ohio State University, Columbus Ohio, is working on canine distemper virus infection in germ-free dogs with associated demyelinating encephalitis, a viral model of MS. Canine distemper is a highly contagious, natural viral disease, whose pathogenesis involves a lympholytic phase followed by viral dissemination to epithelial tissues such as the lung, gastrointestinal tract, and other organs. Virus invasion of the CNS is a frequent occurrence and fatal encephalitis usually results. The team was fortunate to isolate viral strain R1521 which is unique in that although the virus is neurotropic, it causes a persistent infection and demyelinating encephalitis of the CNS in three week old germ-free dogs instead of the usual acute fatal disease. A number of studies associated with this new model are now underway.

Visna is a demyelinating disease in Icelandic sheep caused by a virus. One of the most interesting aspects of persistent visna infection is the phenomenon of

generating variants (antigenic drift), different from the original infecting virus. Among several tentative conclusions is one that the variants could play an important role in the occurrence of lesions and clinical disease.

Recent light microscopic studies by investigators at the University of Pennsylvania have clearly indicated that the pathological lesions of clinical visna are markedly different from those seen in subclinical infections. When clinical disease appears there are severe focal lesions of spinal cord and brain stem, in which tissue destruction, scarring, and demyelination are prominent. Since the Icelandic sheep model is the only one in which clinical visna disease occurs, it offers a unique opportunity to describe the demyelinating lesion caused by visna virus at an ultrastructural level.

Studies at Johns Hopkins University have shown that the macrophage is an important target cell in this infection. The investigator studies the possible role of proteolytic enzymes and phagocytosis of infectious virus-antibody complexes to establish the macrophage properties which may enhance infectivity of the virus and determine tissue tropism. The ability of infected monocytes to respond to chemotactic stimuli are also studied because of their importance in disseminating virus in vivo.

7. Summary and Future Trends

The size of this subprogram, and the level of research activity supported, from the point of view of its relevance to major neurological disorders, appears to be adequate. Research on latent and slow viruses is of high quality and is well represented in this subprogram.

MUSCULAR AND NEUROMUSCULAR DISORDERS

The Neurological Disorders Program supports research in basic nerve and muscle function and dysfunction with special emphasis on Muscular Dystrophy, Myasthenia Gravis and Peripheral Neuropathies. In May 1982, 149 grants were active at a cost of nearly $14,593,000. There are four program projects: one for basic research in neuromuscular diseases, one for research in muscle regeneration and two clinical research centers for neuromuscular disorders and for peripheral neuropathies. In addition, a collaborative clinical trial on the use of plasmapheresis for the treatment of Guillain-Barre syndrome is underway.

Basic Studies on Nerve and Muscle

Nearly 50% of the funds of the grant portfolio are devoted to basic research on nerves, muscles and their interactions. This included 92 grants, costing $7,539,155 as of May 1982. These studies utilize a wide variety of preparations from simple invertebrate organisms through amphibia, mammals and humans. Physiological, biochemical, anatomical, and molecular biological techniques are being used to determine the macromolecular basis of muscle contraction, the mechanism of excitation contraction coupling, and the function of the muscle spindle system. Studies on nerve are underway to specify the channels, gating mechanisms and ion selectivity involved in nerve conduction. In addition, the program supports work on nerve-muscle interaction. These investigations are to determine both the pre- and post-synaptic events involved in neuromuscular and synaptic transmission. They include the mechanism of transmitter action, storage, release and recycling of synaptic vesicles. The activity of acetylcholine receptors and the enzyme cholinesterase are being examined as well as the changes that can be induced in the efficiency of synaptic transmission. Finally the trophic effects exerted by nerve and muscle upon each other are under investigation.

Invertebrates, with simple nervous systems, large neurons and stereotyped behaviors are exceptionally useful for physiological, anatomical and biochemical studies to determine the cellular and eventually the molecular basis of behavior. The crayfish is an ideal preparation in which to examine the response to stretch. The tips of the dendrites in this crustacean's stretch receptor undergo distinctive morphological changes under stretch in comparison with the relaxed state. These changes are described as "beading" and involve alterations in the distribution of the intramembrane particles seen in freeze fracture replicas. Furthermore, the dendrites of the sensory neurons in the stretch receptor have been shown to receive only GABA mediated inhibitory synapses. These receptors are an ideal structure in which to unambiguously identify GABA synapses and to anatomically characterize the pre- and post-synaptic membranes.

Tissue and organ culture is another way of simplifying the nervous system for easier analysis. Studies of development of neuromuscular junctions of the toad and rat in tissue culture are designed to elucidate the roles and mechanisms of synaptic connections. Functional synaptic transmission has been demonstrated to precede and in fact to be prerequisite for the accumulation of receptor molecules on the post-synaptic membrane. There are definite species differences. Toad nerves do not induce receptor accumulation on rat muscle, and neither do rat nerves. Finally, no loss of extrajunctional sensitivity is seen with innervation, but the junctional sensitivity increases further.

In different but related studies, immunocytochemical methods have shown that a form of actin (one of the muscle contractile proteins) is highly concentrated at the neuromuscular junction. It is present in developing muscle before the post-synaptic fold forms and may play a role in the receptor aggregation during the formation of the neuromuscular junction. Investigations on the role of calcium in muscle contraction continue to yield new information. Electrical stimulation of skeletal muscle fiber leads to the release of calcium stored in the sarcoplasmic reticulum which then activates muscle contraction. This work utilizes frog muscle, and the investigators have shown that the sarcoplasmic reticulum senses the tubular membrane potential by charge movement alone. New optical dyes are being designed to measure both membrane potentials and the amount of free calcium present in muscle cells during activation. Previous optical measurements have been demonstrated inaccurate due to the interaction of the dyes with the living system.

Although it has been known for some time that both nerve and muscle are affected in many ways when their normal interaction is interrupted, the causes of these changes are still being documented. Evidence suggests that trophic influences of nerve on morphologic, physiologic and metabolic properties of skeletal muscle are mediated in part by muscle activity and in part by trophic substances which are carried by axonal transport. In order to investigate the mechanism of both of these processes, a model system for the study of protein turnover in cultured muscle has been set up for the investigation of trophic influence and muscle activity on protein synthesis and degradation. A trophic protein, sciatin, purified from nervous tissue, has been shown to enhance the morphological development and to promote the maintenance of skeletal muscle cells growing in tissue culture. In addition, this protein has been demonstrated to increase both the number and density of acetylcholine receptors incorporated into the membranes of these muscle cells.

The overall objective of the muscle transplantation and regeneration project is to learn about mechanisms by which a grafted muscle becomes reintegrated with the nervous and vascular system of the host. Studies during the past year have shown that any muscle precursor cells that may be present in the central ischemic zone of muscle grafts do not undergo DNA synthesis. Investigators have demonstrated that better anatomical distribution of nerve fibers accounts for improvement in nerve-intact grafts compared to standard grafts. A histochemical procedure has been developed to distinguish between the arterial and venous ends of capillaries during the revascularization of free muscle grafts. The major problems in clinical grafting of skeletal muscle are to determine how muscle can best adapt to ischemia during the early post-transplantation period and what mechanisms are important for subsequent revascularization and reinnervation of transplanted muscle. These investigations are directly targeted to such problems and the results obtained can be quickly translated into modifications of current surgical techniques for transplanting skeletal muscle tissue.

Muscular Dystrophy

Muscular dystrophy is a group of chronic, progressive, genetically determined diseases characterized by weakness and wasting of the voluntary muscles. The rate of progression varies markedly from type to type. It is estimated that some 200,000 men, women, and children in the United States are suffering from some form of this disease. Nearly two-thirds of the known victims are children

between the ages of 3 and 13. There is no effective treatment for muscular dystrophy itself. To date, none of the wide variety of diets and drugs administered to patients has shown a significant or lasting effect on the course of the disease. Physical therapy has limited value in delaying contractures but does not otherwise affect the course of the dystrophic process. Antibiotics may prolong the lives of children who would otherwise succumb to respiratory infections. In fiscal year May 1982, 28 grants providing nearly $3,628,533 were awarded in the Muscular dystrophy sub-program, including one program project.

In Duchenne dystrophy, the affected striated muscle is characterized by the presence of scattered foci of degenerating myofibers. Within these foci, numerous myogenic cells in various stages of regeneration represent the potential of the muscle for repair. In older patients, the process of muscle regeneration becomes abnormal and eventually has no influence on the clinical progress of dystrophic degeneration. Studies initiated to test the hypothesis that later regenerative failure is due to a direct effect upon the myogenic stem cell revealed that, contrary to established opinion, induction of muscle competence in somites is a two-phase process. First the myotome is induced and gives rise to a postmitotic contractile rudiment. Then proliferatory stem cells (myoblasts) arise which ultimately develop into musculature. These latter cells are derived from the dermatome. A myoblast-fibroblast modulation is proposed to account for the characteristic loss of regenerating stem cells and simultaneous increase in interstitial fibrosis. Developmental studies to verify this are underway.

Hereditary muscle disorders closely resembling human muscular dystrophy, have appeared in a number of animal species, including hamsters, chickens and rats. These animal models allow scientists to perform controlled experiments which cannot be carried out in human beings.

Hereditary muscular dystrophy in chickens has been postulated to be the result of a primary intrinsic defect in the differentiation of fast twitch skeletal muscles due to the absence, reduction or alteration of a muscle cell membrane receptor for a thymus derived secretory product. The subsequent blockage in muscle cell differentiation or inherited immune abnormalities would then result from a secondary development of autoimmune pathology.

The genetically dystrophic chicken is also being utilized to develop chemotherapeutic drugs. Muscle cells from embryonic chickens are grown in a culture to provide an in vitro assay system in which to study the potential efficacy of specific classes of drugs with various modes of action upon muscle growth, protein turnover and cytochemistry. Inherent practical problems which have impeded the intensive description of muscle growth and protein turnover with drug intervention in whole muscle from intact animals are circumvented with these cultured cells.

Myasthenia Gravis

Myasthenia Gravis (MG) is a chronic neuromuscular disorder characterized by progressive weakness and abnormally rapid fatigue of the voluntary muscles. Twenty years ago about 30% of the patients died within 2-4 years of the onset of the disease and many of those that lived were severely disabled. Today mortality

is less than 5%, and many patients can live relatively normal lives despite the presence of the disorder. In fiscal year 1982, 13 grants were active providing $1,261,075.

The objectives of most of the projects relevant to myasthenia gravis are to determine mechanisms governing the synthesis and assembly of the acetylcholine receptor, to understand the structural basis of acetylcholine receptor function and to elucidate the pathological mechanisms of the disease.

Basic research on MG has utilized such diverse animals as electric fish whose electroplaques contain relatively large quantities of acetylcholine receptors, snakes that produce toxins which specifically bind to these receptors, and rats immunized against purified acetylcholine receptors that develop symptoms much like humans having the disease. A radioimmunoassay was developed for detecting antibodies against acetylcholine receptors and utilized to find these antibodies in animals immunized against purified acetylcholine receptor. Using this assay, it was possible to detect antibodies against human acetylcholine receptor in sera from patients with myasthenia gravis. These studies have demonstrated that myasthenia gravis is an autoimmune disease in which circulating antibodies against a person's acetylcholine receptor molecule have arisen and damaged neuromuscular conduction resulting in muscle weakness and fatigability.

There are still several outstanding problems with understanding this disease. The causative factor in the production of circulating antibodies is not understood. In addition, the relation between the presence of antibodies and impairment of neuromuscular transmission is not a simple one. It is not understood why some patients with severe symptoms of the disease lack or have a low level of circulating antibodies and why the effects of the antibodies vary from one muscle to another.

A syndrome quite analogous to myasthenia gravis can be produced in several strains of mice which show significant variation in the incidence of paralysis. The difference between species, known as high and low responders, has been shown to involve the immune system rather than reflect a difference in the target neuromuscular junctions. Examination of these different strains of mice may help to understand the factors which lead to manifestation of the human disease. Moreover, these studies may shed light on the genetic mechanisms underlying myasthenia, degradation of acetylcholine receptors and the manner in which receptor binding results in paralysis.

The recently developed technique for making monoclonal antibodies offers an ideal tool with which to investigate the relation between antibody specificity and pathogenic effect. With monospecific antibodies it is possible to define the antigenic sites that mediate receptor modulation, and test the ability of these antibodies to induce experimental autoimmune myasthenia gravis in animals.

Several relatively successful treatments to relieve the symptoms of myasthenia gravis are presently in use. These include drugs which block cholinesterase activity, immunosuppressants, thymectomy, which prevents production of antibodies, and plasmapheresis, which removes antibodies from the blood. However, the specific information being obtained on the etiology of the disease should yield not only far more precise and effective treatment, but may even lead to the prevention of MG, as well as other autoimmune diseases.

Peripheral Neuropathies

The peripheral neuropathies are common and serious health problems often associated with prolonged morbidity. The majority of the affected population are diabetics. There are approximately three and a half million diabetics in the United States and 10% of them have symptoms of painful burning, numbness, weakness or paralysis of the extremities. Male diabetics often become impotent, a defect which may be due to autonomic neuropathy or angiopathy. The direct cause of these neurological disorders is not known, and no therapeutic measures are available. The Neurological Disorders Program especially encourages research in this area. In addition to diabetic neuropathy, the Program supports research in steroid and toxic neuropathy and in Guillain-Barre' syndrome. During May 1982, twelve regular grants and one clinical research center program project in the general area of peripheral neuropathy were awarded at a cost of $1,931,614.

Diabetic rats kept normoglycemic showed no significant difference in the rate of fast axoplasmic transport compared to controls. In severely hyperglycemic animals, the downflow rate was significantly reduced. In addition, a selective staining technique for the smooth endoplasmic reticulum in nerve fibers was developed. Combining this staining technique with high voltage electron microscopy allows the examination of the 3 dimensional structure of the smooth endoplasmic reticulum. This work is important for correlating changes in the presumed morphologic substrate for axoplasmic transport with the abnormalities identified in hyperglycemic rats.

Idiopathic polyneuritis, known as Guillain-Barre' syndrome, is presently the most common cause of acute severe generalized paralytic disease in people. Although a relatively uncommon condition, affecting the population at a reported annual prevalence of 1-1.6 cases per 100,000 population, it has recently come to public attention in the United States as a presumed complication of vaccination against "swine flu".

Investigations on Guillain-Barre' syndrome have demonstrated that rats are far more suitable animals in which to study experimental allergic neuritis, a model for the disease, than are rabbits, guinea pigs or monkeys. Furthermore, a protein of peripheral nerve myelin has been identified as the neuritogenic antigen when present as a lipid-protein complex. These studies should eventually provide the insight needed to elucidate the induction and possible suppression of the Guillain-Barre' syndrome in humans. Finally, a collaborative clinical trial on the use of plasmapheresis to treat acute Guillain-Barre' syndrome is underway and the results should be available by 1983.

OTHER NEUROLOGICAL STUDIES

This section consists of three main categories of research projects:

Neural Aspects of Learning and Behavior
Disorders of Other Senses with Emphasis on Pain Research
Neuroendocrine Studies

The research activities in these three categories are described in the following reports.

NEURAL ASPECTS OF LEARNING AND BEHAVIOR

In this category there are 4 projects. These projects are directed towards the identification of anatomic and morphological substrates in the central nervous system that influence behavioral alterations. Investigations are conducted to assess possible behavioral consequences of genetically determined traits as related to structural organizations in several strains of animal models. A question is being tackled of whether, or not, in children, the degree of lateralization of handedness is related to intelligence. Towards this end, the correlation of degree of handedness with learning ability is being investigated. The other aspect of learning and behavioral processes is related to the identification of macromolecules and biochemical markers that may be important in establishing long-term memory. In these studies changes in specific proteins during acquisition of new behavior have been observed. It is hoped that eventually such studies may help explain the mechanisms of learning, memory and behavioral manifestations.

DISORDERS OF OTHER SENSES WITH EMPHASIS ON PAIN RESEARCH

In this category there are 28 projects. About two-thirds of these projects are related to pain and pain mechanisms. A narrative on this subject is also included. Other projects in this area are related to motor control, neural mechanisms subserving position sense, and sensory coding. The emphasis is upon ascending spinal pathways conveying static position signals, the identification of the types of receptors that contribute to these signals and the central representation of these signals within the brainstem, thalamus and sensory cortex. The hypothesis is being tested about the nature of segmental and supraspinal motor control systems and the variables that are controlled by segmental reflex areas. Studies are also designed to investigate the neural processes underlying the initiation and guidance of voluntary limb movement to answer questions, such as, what parameters of movement are specified by central programs and how are these parameters expressed in the neural activities of the major motor systems. Also, what role does afferent information play in the initiation and control of movement and how can this information be used by the nervous system to alter existing programs to better achieve the behavioral responses.

PAIN

Neuropeptides and Receptors

Our knowledge of synaptic transmission in the spinal dorsal horn is extremely limited both in terms of agents and biophysical features. It is suggested that at least part of the reason is the difficulty in recording in vivo from the relatively small cells of the region intracelluarly for long enough to do systematic biophysical and pharmacological studies because of movements due to respiration and cardiovascular pulsations. This project is designed to overcome these difficulties through the use of a slice preparation of the dorsal horn that theoretically would permit study under the physically more stable conditions of a bath. The long-term aim is to determine the transmitter identity and synaptic circuitry of neurons in the spinal cord that are involved in central mechanisms of pain. Both biophysical and pharmacological studies are outlined. The former would be used to determine general characteristics of cells such as input resistance. The pharmacological manipulations are being used to test for the effects of peptides (substance P, vasoactive intestinal peptide (VIP), cholecystokinin, enkephalin) and other agents such as opiates.

The demonstration of stereospecific binding of morphinoid opiates to receptors in the brain suggested the presence of endogenous ligands for these receptors. This presence was confirmed and two closely related, endogenous ligands, Met-enkephalin and Leu-enkephalin were isolated from porcine brain and sequenced. A series of conformationally restricted analogs of Met - and Leu - enkephalin are being synthesized, tested for biological activity, and studied by various physical techniques to elucidate their conformations in aqueous solution. Comparisons of conformational features within the series and correlation with receptor binding affinities and other in vivo and in vitro activities are being used to isolate the key conformational requirements for binding and/or transduction. Since it is becoming increasingly clear that multiple opiate receptors exist and since these receptors can be expected to have different conformational requirements, the information derived from the conformationally restricted analogs of this study will be used in the design of more potent and more specific analogs. These enkephalin analogs are being tested for their opiate activities using rat brain receptor binding, guinea pig ileum, rat tail flick, and other assays.

Pharmacological Studies of Pain Systems

Stress-induced Analgesia: several projects are directed towards psychophysical analysis of stress-induced analgesia. For example, it has been noted that acute exposures of a severe stressor can result in analgesia. Repeated exposures result in a progressive decline of the analgesic responses, in much the same manner that the pituitary-adrenal responses to stress show adaptation. Virtually every physical stressor increases plasma levels of B-endorphin as well as ACTH and corticosterone however, not all stressors produce analgesia Some stressors induce an analgesic response that is sensitive to opiate receptor blockade by naloxone, others cause a nonnaloxone sensitive analegsia. The proposed psychophysical experiments will assess whether the sensory changes induced by various stressors are specific to the modality of pain or whether they are accompanied by deficits in auditory and/or visual acuity as well.

Another study is concerned with stress analgesia and the possibility that stress is a physiological trigger to endogenous analgesia systems. Much evidence is cited to support the conclusion that such analgesia systems do exist in the central nervous system. Far less information is available concerning the circumstances that normally call this system into action. Stress seems to be such a trigger, but its opioid basis has been in doubt. The thrust of this work has been to show that both opioid and nonopioid analgesia systems occur. Using a single stressor, footshock, the investigators have obtained reliable naloxone-sensitive and naloxone-insensitive stress analgesia. By applying other criteria for opioid involvement (sensitivity to low dose naloxone antagonism, tolerance development with repeated application of stress, and cross-tolerance with morphine), they found a consistent pattern of results. According to all criteria used so far, the one form of stress analgesia is opioid, the other not. It is concluded that some forms of stress are adequate triggers for an opioid analgesia system. Other forms appear to make use of some parallel system whose neurochemical basis remains unknown.

Pharmacological studies of descending spinal pathways involved in the modulation of pain sensations are being pursued. Evidence exists showing that neurons in the raphe magnus, many of which are serotonergic, are activated by acetylcholine and inhibited by noradrenalin. These observations are extended by determining the functional significance of these connections and their relevance to analgesia. The hypothesis is tested that cholinergic neurons project to the nucleus raphe magnus (NRM) and this connection produces analgesia. Tail flick and hot plate tests are being used to assess analgesia after microinjection of one of a series of cholinergic agonists or cholinesterase inhibitors. In some cases, either nicotinic or muscarinic antagonists will be injected to determine the specificity of the effect and the receptor type.

Peripheral neural mechanisms of pain adaptation and of primary and secondary hyperalgesia are being studied in monkeys and humans. Small increments and decrements in skin temperature are superimposed on different base temperature before, during, and after mild skin injury consequent to a single heat stimulus. Test stimuli are applied either within the area of injury or to a nearby area. Incremental and decremental detection thresholds will be measured in both monkey and human subjects, using a two-alternative forced choice procedure and an escape-tolerance detection task. In addition, human subjects will make repeated magnitude estimations during the course of evoked pain sensations. Responses to the same heat stimuli of mechanothermal nociceptive A and C fibers will be recorded from peripheral nerves of anesthetized monkeys and of awake human subjects. Objective measures of thermal sensitivity (e.g.,detection thresholds) in monkeys and humans are being compared with subjective measures of pain in humans and, in turn, with response sensitivities of nociceptive A and C fibers in both monkeys and humans during pain adaptation and during the development of primary and secondary hyperalgesia.

Neural Pathways in Transmission of Pain

Studies of neurochemical neuroanatomy in the brainstem nuclei critical in nociceptive perception in the spinal cord are being pursued. It has been clearly demonstrated that serotonergic and enkephalinergic neurons located in the nucleus raphe magnus of the brainstem project downward into the dorsal horn of the spinal cord and modulate nociceptive thresholds. Using neuroanatomical techniques the

investigators are determining retrograde transport and immunohistochemical localization to know which neurons are serotonergic, which are enkephalinergic and which co-secrete serotonin and enkephalin. They are particularly interested in the neurochemical coding at the EM level in the cord, and also propose to define the location of opiate action in the periaqueductal gray by similar approaches.

Several projects are directed towards mapping the sensory conducting fibers in the spinal cord, brainstem and other parts of the nervous system. For example, one investigator is analyzing in detail the afferent and efferent connections of spinal and brainstem somatosensory systems by sorting processes that occur as fibers from the dorsal column nuclei (DCN), spinal trigeminal nerve, and lateral cervical nucleus diverge and reassemble upon entering the diencephalon. This strategy is providing data on individual neurons with the DCN regarding each neuron's response properties, its precise location, its shape and size.

Another investigator is continuing his electrophysiological, morphological, and immunocytochemical studies on spinal cord sensory processing systems. These studies are designed to refine our knowledge of the small fiber afferent system in its early stages of processing within the spinal cord. This work is important for health-related problems because it attempts to establish the synaptic arrangements associated with pain and related mechanisms. Now that the signalling of tissue damage and tissue disturbing stimulation is established to come from specialized sense organs (nociceptors), the central connections of such neurons take special importance. Understanding both the symptomatology and the pathophysiology of pain requires understanding of the neural circuitry involved. From the standpoint of therapy, the synaptic stations and chemical intermediaries at synapses have a special significance since it is at the points of synaptic transfer that most potent, neurally-acting drugs produce their effects. The possibility of selective drug therapy for pain and its disorders will be greatly enhanced if we understand the pathways and synaptic mechanisms peculiar to the sensation.

Neurophysiological and Psychophysical Studies of Pain

There has been considerable interest in central mechanisms of pain sensation. The fact is, however, that pain in the vast majority of cases arises from lesions outside the central nervous system. These diseases include causalgia, reflex sympathetic dystrophy, neuromas, chornic degenerative disc disease, nerve entrapment, and tic douloureaux. Studies of peripheral neural mechanisms are addressing the question of how and why pain signals are generated in patients. The ultimate aim of this research is to learn how to prevent the abnormal pain signals from being generated in the first place. The investigators have laid the groundwork on mechanisms of cutaneous pain in normal and injured skin. They are now studying how pain signals are produced in injured nerves. The injuries at first will consist of nerve transections with and without resuture, and nerve crush. In this way they are trying to understand how and why neuromas, nerve crush and nerve regeneration cause pain. They are also attempting to simulate other types of nerve injury that appear to be associated consistently with chronic pain. A final objective of this work is to determine the basis for how electrical stimulation relieves pain. This therapeutic intervention represents one of the most significant tangible advances in pain therapy of the past decade. It works well, however, in a small number of patients. Better

understanding of how it relieves pain may lead to improvement and wider utilization of this technique.

NEUROENDOCRINE STUDIES

Currently this program supports 73 projects related to steroid hormones, neuropeptides and interaction of these endocrine systems with monoamine neurotransmitters. Most of these projects deal with the identification of hormone receptors and neurosecretion. Also included are related phenomena such as synthesis, storage, release, transport, conversion, inactivation, regulation, and characterization of the neuroendorine peptides in the brain, hypothalamus and pituitary. Some projects study neuroendocrine functions as related to behavior, thirst, hunger, body weight regulation, circadian rhythms, stress, temperature regulation, etc. The total expenditure in this subprogram is $5,561,358.

During the past few years many separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Almost without exception, the highest concentration of these substances is in the hypothalamus, with particularly high concentrations in the neurovascular zone of the median eminence. Several of these peptides have clear functions in relation to anterior pituitary control; others, although shown to influence hormone secretion, may function primarily in other regions of the brain related to sensory conduction, pain mechanisms, and behavioral responses. Receptors for many of these substances are now being searched for in the brain. Pathways linking peptidergic systems are currently under investigation using neuro-anatomical tracing techniques and immunocyto-chemistry.

Occurrence of Neuropeptides

Several projects are investigating the distribution of several biologically active peptides in the brain, spinal cord, and pituitary gland. The following peptides are being be studied: Substance P, neurotensin, thyrotropin releasing factor, gonadotropin releasing factor, somatotropin releasing factor or somatostatin, melanotropin release inhibiting factor, alpha-melanocyte stimulating hormone, the opioid peptides: enkephalins and endorphins, etc. The peptides are being localized with the help of specific antibodies. Thus the sensitivity and specificity of the immunochemical binding is combined with the structural resolution of light and electron microscopy. This permits precise topographical localization and mapping of the peptide-containing cells, pathways and synaptic contacts in the brain. Most of the peptides to be studied have been discovered only recently. Initial work indicates their widespread distribution throughout the body, but especially in the nervous and endocrine systems. They may function as neurotransmitters, modulators of neurotransmission, regulators of hormone release from the pituitary gland, or as neurohormones released directly into the blood stream. In order to conduct meaningful physiological studies with these peptides, knowledge on their precise cellular and subcellular localization as well as topographical distribution in the central nervous system will be essential.

Peptide Receptors

The role of peptides in neurobiological function has received increasing attention in recent years. It appears that most peptides are distributed widely

throughout the brain and act by attachment to peptide receptors to initiate neurobiological events; these effects result in neurophysiological, biochemical, and behavioral manifestations. The presence of peptides in the CNS has stimulated intense interest in uncovering cellular receptors for them. Current studies are directed at determining whether such receptors exist, the nature of their localization (i.e., presynaptic, postsynaptic, or in blood vessels), whether their distribution coincides with that described for the peptide, and whether more than one type of receptor is present for a given peptide form or forms. At present, save for the opioid receptors, this field remains in its infancy. Identification of two types of opiate receptors according to binding characteristics and by bioassay has occurred in parallel with the demonstration of multiple types of opiate substances present within the nervous system. These observations have served to illuminate the diverse physiologic functions of the endogenous opioids. It appears that there are at least two types of opiate receptors, called mu and delta. It is likely that mu receptors are involved in mediating analgesic responses, whereas delta receptors are involved in eliciting seizure activity and in certain behavioral responses. Endorphin appears to bind to both types of receptors; the enkephalins bind only to mu receptors. Morphine binds predominantly to mu receptors, and it has been suggested that dynorphin, which is vastly more potent, may be the endogenous ligand for the mu receptors. It has been possible to characterize the differential distribution of delta and mu opiate-receptor localization within the CNS by autoradiography and with the light microscopy.

The functional significance of specific prolactin binding sites on ependyma of the rat choroid plexus is being investigated with emphasis towards a possible role for prolactin in the regulation of electrolyte balance between blood and cerebrospinal fluid (CSF). A preliminary electron microscopic autoradiographic analysis of prolactin movement relative to ependyma cytology indicates initial binding of prolactin to ependyma plasmalemma within a very short time. These results suggest that ependyma may be the final target cells rather than a component of blood to CSF transport system for prolactin.

Brain cells are protected from the effects of circulating peptides by the brain endothelial wall, i.e., the blood-brain barrier (BBB). The available evidence indicates specific transport systems in the BBB, similar in nature to carrier systems known to transport nutrients and thyroid hormones, do not exist for peptides. There is evidence, however, that specific receptors for circulating peptides such as insulin do exist on the luminal side of brain endothelia. Peptide binding to the BBB may generate the production within endothelia of second messenger compounds that are released to brain extracellular space. In this way mechanisms would exist for the rapid modulation of brain cell function by circulating peptides, without the peptide actually crossing the BBB. Studies are examining peptide binding and action at the BBB using the isolated cerebral capillary as the primary model system. Three major areas will be investigated. The specific binding to isolated capillaries of such peptides as insulin, enkephalins, vasopressin, somatostatin, angiotensen II, and prolactin are being studied, and second messengers such as cyclic AMP, cyclic GMP, glycine, glutamate, aspartate, or GABA will be investigated which affect the peptide-mediated release of these substances into the brain.

Neurotransmitters and Neuropeptide Secretion

Although it is well known that neurotransmitters play a prominent role in the regulation of hypophyseal hormone secretion, their site of action is unclear. The neurotransmitter effect may be a direct one with the neurotransmitter itself stimulating or inhibiting hormonal release from the pituitary gland. Alternately, its effect may be an indirect one by modulating the release of specific hypothalamic releasing or inhibiting hormones. Studies are being conducted to determine the actions of the neurotransmitter dopamine on pituitary hormone secretion with emphasis on prolactin (PRL) and growth hormone (GH) release and to ascertain whether hormonal secretion is affected by direct (peripheral) action on the pituitary gland, by hypothalamic or higher center actions (central) or by actions at both levels.

There is a great deal of evidence that the biogenic amine, dopamine (DA), affects pituitary function in the human. This effect is more pronounced on PRL and GH secretion. DA has recently been shown to also blunt LH secretion in healthy women and men. An effect on corticotropin (ACTH) and thyrotropin (TSH) in normal subjects is more subtle, but under extreme endocrinologic perturbations it is readily apparent.

Peptide Processing and Degradation

The control of neuropeptide activity by specific peptidases both to regulate production of active fragments from larger precursors and to specifically degrade the active products is an important central issue in neuropeptide function. A promising line of investigation of this phenomenon is proposed for purification of cation-sensitive neutral endopeptidase and partial purification of prolyl endopeptidase. Both enzymes have been characterized in terms of molecular weight, cation sensitivity, pH optimum, sensitivity to inhibitors, regional brain distribution, and peptide bond specificities. Even at this rather early stage of the work, several possibilities of specific biological functions of these enzymes have been suggested. Neutral endopeptidase is enkephalinogenic when tested on alpha-endorphin. Prolyl peptidase cleaves substance P specifically at the single peptide bond that generates two active fragments (C-terminus is much more potently bound to synaptic membranes than sub-P itself; N-terminus is a neurite growth factor). The facts that angiotensin converting enzyme and prolyl endopeptidase have some overlapping specificity and that angiotensin converting enzyme inhibitors given to rats increase brain levels of substance P may indicate the prolyl endopeptidase does function physiologically to control levels of this hormone. The studies designed to produce specific endopeptidase inhibitors using peptide aldehydes may provide both a useful probe of the physiological function of these enzymes and a new class of neuroactive drugs.

Another study is concerned with the investigation of conversion and inactivation of peptide hormones. Two separate series of experiments are planned: (1) those concerned with enzymes involved in conversion as defined by the production of smaller fragments from precursor materials; and, (2) enzymes involved in the breakdown and inactivation of active peptides. Several systems will be studied. In the first, angiotensin(s) will be studied with respect to the two enzymes involved in conversion, namely, renin and the angiotensin-1 converting enzyme. The second group of polypeptides are the lipotropins. The enzymes involved in the cleavage of beta-lipotropin to its individual fragments will be

investigated. Other experiments will investigate the inactivation of LHRH where considerable progress for purification of inactivating enzyme has been achieved. Other studies of a similar type are being conducted with somatostatin and the opioid peptides. Data obtained will be useful for basic knowledge on the formation and metabolism of brain hormones, and for developing analogs with higher potency and longer action which may be important in clinical implication.

Behavioral Responses to Neuropeptides

Learning and Memory

Research on the neurochemical basis of learning and memory has been one of the major concerns in the neurosciences. The theoretical implications of the functions of brain peptides in higher processes of the central nervous system is of considerable interest. Clinical implications of research on neurochemistry of learning and memory are appreciated when it is realized that there is no adequate therapy for memory derangements found in clinical neurology and geriatrics.

Vasopressin (VP), a neurohypophyseal hormone, has been implicated in memory processes of the CNS both in humans and in rats. A large body of data implicates VP in memory processes for active and passive shock-avoidance tasks. Oxytocin (OT), another neurohypophyseal hormone, has been shown to have effects opposite to those of VP on avoidance behavior in normal animals. Indeed, it has been suggested that OT is an endogenous "amnesic peptide". The alleged effects of VP on memory processes in normal rats may be unrelated to its endocrine actions because a VP analog, desglycinamide-lysine-8-vasopressin which has minor antidiuretic, pressor and adrenocorticotropin (ACTH) releasing activities, has effects on avoidance behavior similar to those of VP.

Discovery of the Brattleboro strain of rats (HODI) which exhibits congenital hypothalamic diabetes insipidus allowed another possible test of the hypothesis that VP is involved in CNS processes. These rats lack VP in the brain. These rats are also inferior in acquiring and maintaining active and passive shock-avoidance behavior when compared with normal heterozygous DI rats. The behavioral differences could be obliterated by injections of VP into HODI rats. Studies have found that HODI rats actually show better retention of the aversive component in an approach-avoidance behavioral task than normal animals. The interpretation, based on data gathered on HODI rats, that VP is involved in memory needs a more complete characterization than is presently available.

Feeding Behavior

The central nervous system is known to play an important role in body weight regulation through its control of behavioral, hormonal, and metabolic events. Recent studies in animals have implicated several peptides in the regulation of feeding behavior. CCK, TRH, and insulin are reported to be satiety factors, decreasing food intake, whereas beta-endorphin has been implicated in states of increased food ingestion. The site of action of these peptides in affecting feeding behavior has been presumed to be within the CNS, with controversy over whether this effect is mediated through the ventromedial hypothalamus; interaction with the noradrenergic system has been proposed. Suppression of feeding by CCK has also been reported to be mediated through a parenteral abdominal site.

Another line of investigation suggests that central monoamine system controls the body weight regulation. These studies are based upon an animal model. In genetically obese mice in which abnormalities have been uncovered in catecholaminergic system, the relationship of spontaneously occurring obesity to monoamine function is being investigated. In the diabetes mouse, reduction of central norepinephrine levels improves the obesity syndrome. Experiments are being conducted to explain this phenomenon. And, the question of the effector mechanisms in the central control of body weight regulation is being examined. In the most widely studied models of abnormal weight regulation, rats with either ventromedial or lateral hypothalamic lesions, altered autonomic function is apparent. Data are accumulating to suggest that a change in the sympathetic nervous system may be important in weight changes that follow the lesions. These studies will examine the contribution of central catecholamines to disturbances in autonomic function related to feeding and body weight.

Cholecystokinin (CCK) peptides are present in brain in high concentrations, and CCK and its specific receptors have been shown to be localized in such areas as cortex and hypothalamus. Recent evidence strongly suggests a role for brain CCK in the control of feeding behavior. CCK, when injected into the cerebral ventricles of sheep, acts as a highly potent agent in suppressing feeding behavior. Of real physiological significance is the finding that satiety can be blocked by injection of CCK antiserum into the CSF. It is hypothesized that CCK is released in the brain during feeding, possibly secreted into the ventricular system and transported via CSF, and acts on CNS receptors involved in the elicitation of satiety. Investigations are being conducted that will determine rates of release of CCK into CSF during hunger and satiety and determine sites of release as well as sites of action of brain CCK in causing satiety. Thus, these experiments will provide additional information necessary to establish the physiological role of CCK in brain in the control of feeding behavior.

In another study the neuroanatomical organization of areas of the nervous system are being traced which are responsible for the control of food intake and body weight regulation. Although it has been known for some time that damage to certain areas of the hypothalamus can lead to obesity in an otherwise normal experimental animal, the neuroanatomical organization of these areas, which include the ventromedial (VMN), arcuate (ARC) and dorsal premammillary (DP) nuclei, is not well understood. Recent biochemical evidence based on chemical stimulation and measurement of catecholamine levels has also implicated the paraventricular nucleus (PVN) and the median eminence (ME). The present series of experiments are aimed at 1) elucidation of hypothalamic organization in normal rats and 2) determination of possible anatomical and biochemical abnormalities in the brains of genetically obese rats. Normal cytoarchitectonic features as well as neural connections of VMN, ARC, DP, PVN and ME will be studied. In humans a relationship exists between obesity and certain diseases. Elucidation of the neuroanatomical pathways involved in the control of food intake and body weight regulation as well as demonstration of abnormalities in the brains of genetically obese animals may be of use in therapeutic approaches to obesity.

Temperature Regulation

Temperature regulation represents a complex interplay of several causative agents and/or pathological conditions. Circadian temperature cycle may occur as a

result of hypothalamic injury (tumors, cysts, etc), imbalance of neuropeptides in the brain affecting thermoregulatory system, transport of pyrogens in cessation or induction of fever, hormones and neurotransmiter release, calcium/sodium imbalance in the hypothalamus, etc.

Hypothalamic lesions produce devastating effects in man. Many of these lesions are caused by tumors or cysts arising from tissue at the base of the brain or the floor of the cranial vault and can be successfully treated if detected in time. The classic signs of hypothalamic injury are useful in making the diagnosis, but many of them occur late in the history of the injury. In the course of these studies on fever mechanisms in patients and subhuman primates with neurological injury, the hypothesis was developed that the disruption of the circadian temperature cycle may be a useful diagnostic sign of hypothalamic dysfunction. The plan is proposed to test this idea by observing circadian temperature cycles in monkeys in which hypothalamic lesions are progressively produced, as an analogue of the progressive injury that occurs in man. Temperature cycles will be recorded in patients with known or suspected hypothalamic injury to correlate the temperature cycles with evidence of central lesions. Information from these studies may be useful in the diagnosis of hypothalamic disorders.

Previous research on this project has shown that the study of clinical cases of dysthermia can provide information that is directly useful to the clinician, and it can serve as a guide to important research problems. Patients are being studied to learn whether, as described above, circadian temperature cycles are altered by hypothalamic lesions. Also other patients have been tested with CNS sarcoid disease, Wernicke's encephalopathy, Fröhlich's syndrome, fever of unknown origin, accidental hypothermia, heatstroke, drug fever, and CNS disorders due to perinatal anoxia. These studies may provide a great deal of return in terms of direct applicability of the data to health sciences, and clinical application.

TAB 5.A -- EPILEPSY BRANCH -- EB/NDP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Epilepsy Branch, NDP

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

RESEARCH PROJECTS

ANNUAL REPORT
October 1, 1981--September 30, 1982

Epilepsy Branch
Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health

The Epilepsy Branch committment to the prevention, diagnosis, and treatment of epilepsy continues as its goal. Through its Antiepileptic Drug Development Program, the Branch supports drug development in selected areas where there is minimal commercial interest and where reasonable prospects for successful development of effective agents exist. These activities were highly recommended for continuation by an ad hoc review committee in February 1982. They are supported by the contract and direct operations mechanism although the Branch proposes to launch a major new clinical trial (Prevention of Posttraumatic Epilepsy) by the Cooperative Agreement mechanism. The Branch also intends to broaden the range of the drug development program by utilization of the grant mechanism.

Several personnel changes occurred among the Epilepsy Branch professional staff during this year. Lawrence D. Smith, M.S., retired from his position as Pharmacy Consultant after many years of service with the Branch. This position was filled by Frank Nice, M.S., who recently completed graduate work at the University of Arizona. Qu Zhiping, M.D., a WHO Neurosciences Fellow, returned to Shanghai at the end of the year. He will apply many of the techniques learned at the Branch in setting up the first intensive monitoring system of epilepsy in China. Dr. Qu Zhiping will be replaced by Yu Liyun, M.D., also of Shanghai. Also during the year, Salvatore Piredda, M.D. joined the Branch as a guest worker to study neurochemical mechanisms of anticonvulsants.

The NINCDS Antiepileptic Drug Development Program has continued to be effective in interesting pharmaceutical companies to pursue the development of new drugs for the treatment of seizures. The screening project received nearly 1,000 chemicals to determine possible anticonvulsant activity. These chemicals were evaluated by its contractor, the University of Utah. Ninety day rat and dog toxicity studies continued at Southern Research Institute under contract, with compounds from six firms having been evaluated to date. The first compound submitted by an academician was also evaluated this year. In continuing a major effort, Epilepsy Branch staff worked closely with the Contracting Officer, NINCDS, to utilize a master agreement with task orders for clinical trials of antiepileptic drugs. This support mechanism provides the opportunity to evaluate new drugs in any of the seizure classifications without the lengthy procedures normally associated with awarding research contracts. Last year, a task order was awarded for the pharmacokinetic evaluation of Progabide in addition to two task orders for the clinical evaluation of this drug in partial seizures. This year, two task orders were awarded for the clinical evaluation of two new antiepileptic drugs. This major undertaking in clinical evaluation of a new drug represents the reinstatement of the clinical thrust of the Antiepileptic Drug Development Program.

The Epilepsy Branch is involved in a multicenter collaborative study, sponsored by Hoffmann-La Roche, Inc., designed to evaluate the relative short-term safety and efficacy of Nitrazepam and ACTH in infantile spasms. This study is intended to serve as the basis for a New Drug Application designed to make Nitrazepam

available in the United States for the treatment of this disorder. Also, Flupirtine, one of the first compounds to be successfully screened through the Antiepileptic Drug Development Program, is presently under clinical evaluation as a potential antiepileptic drug at the Clinical Center, NIH.

The pharmacology laboratory of the Epilepsy Branch continues to provide support for the Antiepileptic Drug Development (ADD) Program and to study the metabolism of anticonvulsant drugs. The laboratory has developed a method of analysis for Progabide and its active metabolite by high pressure liquid chromatography (HPLC). This method is being used in the Branch's clinical efficacy studies for this drug. There are also efforts underway in developing new in vivo and in vitro models for evaluating the pharmacologic activity of new anticonvulsant drugs.

The endogenous receptors, benzodiazepine and GABA, are being investigated as possible in vitro epilepsy models. The chemical and electrical bonded seizure model is also being investigated for use in screening potential antiepileptic drugs. Data derived from these potential models will be correlated with the results obtained from the standard Maximal Electroshock and subcutaneous Metrazol epilepsy models. In vitro models are being used in studying both metabolic pathways and potential drug-drug interactions. Studies examining the interaction of phenytoin-primidone and phenytoin-carbamazepine are underway using rat microsomal enzymes. The rat will be useful in delineating the mechanism of the interactions.

Through many different means, the Epilepsy Branch in FY82 has remained actively involved in all aspects of epilepsy activities. Contracts have been awarded or are already ongoing to evaluate antiepileptic drug actions in small animal and monkey models as well as part of clinical trials involving human volunteers and patients with epilepsy. Comprehensive Epilepsy Programs have supported applied research as well as having coordinated research and teaching with health care services related to persons with all types of epileptic seizures within defined geographic areas. The Branch is currently aiding in the planning and organizing of the Epilepsy International Symposium to be held in Washington, D.C. in 1983. Many national and international visitors participated in exchange of ideas and concepts with Branch personnel during the year. Also, the Branch has maintained and broadened relationships during the past year with drug companies to foster the development of new and novel antiepileptic drugs and also with national and international epilepsy societies to assist in the dissemination of information on epilepsy.

While substantive efforts continue in the development of new antiepileptic drugs, major advances were made in FY82 in understanding the role of GABA and the benzodiazepine receptor complex in neuronal activity. Hopefully, these developments will provide more insights for the treatment of more than two million Americans suffering from epilepsy.

In FY82, the NDP received 136 applications for research and support of convulsive and related parxysomal disorders, of which 108 were approved and 18 funded for a total of $2,488,558. Of the funded applications, 12 were new or supplemental awards for $1,279,656. There are currently 93 active grants totaling $9,943,510.

Four-fifths of the grants supported by the Epilepsy Branch involve basic research on processes responsible for generation, spread and control of abnormal discharge in animal tissues. The remaining grants are dedicated specifically to the study and control of seizures in humans.

Approximately half of the grants have as their primary objective to understand the basic mechanisms which are responsible for the generation and spread of epileptiform discharges. A basic question to be answered is whether the neurons involved in epileptiform discharges are normal neurons in an abnormal aggregate or if the cells in such an aggregation which produce epileptiform discharges are themselves abnormal. How these cells connect and intercommunicate with each other to produce these discharges is not known. The attention in basic physiology research is focused on excitatory post-synaptic potentials (EPSP), which is the initial event of an epileptiform discharge, and the inhibitory potential (IPSP) responsible for control of the EPSP. It has been shown that a normal cell can produce a "burst" or EPSP. Other cells, which have been shown to be inhibitory, can also produce bursts. Experiments on hippocampal slices have shown the IPSP, which is an important control mechanism, can be blocked with agents such as picrotoxin. If this blocked neuron is then stimulated to produce an EPSP, the impulse is transmitted to the axon with inhibition. With repeated EPSPs, it has been shown that there is a change in the shape of the dendritic spike, resulting in a facilitation of transmission of these impulses to the axons. Other studies have shown that penicillin works on synapses, blocking the IPSP, producing synchronous activity of cells.

Single cell physiology is inadequate to explain the spread of an epileptiform discharge. Investigators are currently studying different pathways for cellular communication of nervous activity. What makes a combination of cells, which are apparently normal, act together to produce an abnormal discharge? There are two aspects to the answer: the number of connections between the cells and the strengths of coupling between cells. There are at least four ways that neurons can conduct electrical activity. In addition to conducting impulses by chemical neurotransmission, cells may be coupled electrotonically by so called "gap junctions." In addition, cells can excite their neighbors by the field potential of apposing membranes. Finally it is also known that accumulation of extracellular cations, such as potassium and barium, contribute to synchronization of cell

activity. Investigators have shown that few cells can be coupled electrotonically. This electrotonic coupling exists in both the neocortex and the CA1 region of the hippocampus. Although research indicates that the number of such connections are relatively small, electrontonic coupling does contribute to the synchronization process. Further research has shown that there is a much higher percent of cells electrotonically coupled in the newborn cortex, indicating that such coupling may be very important in the development of neuronal activity in the cortex.

Histopathological studies on tissues from epileptic foci show a loss of dendritic spines, with development of nodules which gradually spread to other cells. In addition, there is a collapse of the dendrite system around a single stalk. Other investigators have observed a development of large nodules around shafts of glia, with glial shortening resulting in glial scars. In addition, the mossy tufts of neurons in the CA3 region in kindled rats have a strikingly different appearance than in normal rats. The dendritic shafts from seizure-prone gerbils show fewer dendritic spines than animals that are not seizure prone. Vascular changes have been noted in patients with epilepsy whose tissues have been examined after surgical removal. In up to a third of all tissue, there have been microaneurysms or some other abnormality in the vascular tree with extravasation of blood into normal nerve tissue.

Other investigators are attempting to determine the role of astroglia and their relationship to seizure activity. It is thought by some observers that astroglia act as a potassium buffer, but this research is in its early stages. It is known, however, that astroglia swell in the presence of brain edema and therefore take up water. This function is mediated by carbonic anhydrase and the sodium-potassium ATP pump. Other studies on the neurochemistry of epilepsy have shown that in the presence of seizures, there is an accumulation of glutamate with ammonia intoxication resulting in a decrease in GABA content, high intracellular potassium, and CO_2 imbalances.

Inhibition of excitatory activity within the neuron is mediated by chloride permeability. Cells which are principally inhibitory in nature, the so-called interneurons, have been shown to have higher concentrations of glutamic acid decarboxylase (GAD). There are a variety of ways that inhibitory control can be lost. Investigators have shown that there can be a decrease in the number of inhibitory cells following injury, hypoxia, or other insults such as freezing, etc. Other investigators have shown that GABA synthesis can be decreased by biochemical means such as pyridoxine deficiency and hyperbaric oxygen. GABA release can be diminished by toxins, and GABA receptors can be inactivated by drugs such as bicuculline, penicillin, and picrotoxin. Alterations of the chloride gradient, for example, by replacing chloride with barium, can interfere with the chloride pump and result in loss of inhibition. Investigators have shown that in the alumina cream model, the amount of GAD and the number of GABA releasing terminals in the cortex are significantly reduced. Other studies have shown that cells with a high GAD content seem particularly susceptible to injury, hypoxia and necrosis. In a strain of rats susceptible to seizures when exposed to white noise, it has been shown that GABA binding is markedly reduced in certain areas of the brain. Also in some patients it has been noted that there are large decreases in GAD content

as well as in GAD binding.

Neuropeptides probably play a significant role in the generation or control of abnormal discharges. For example, somatostatin increases the excitability of CA1 cells in the hippocampus similar to the effect of glutamate. More often, it has been shown that there is a change in the pre-synaptic terminals which may be an indirect effect of the hormone. The peptides arginine-vasopressin and oxytoxin increases cortical excitability and can induce seizures. Arginine-vasopressin in the hippocampus can evoke increases in excitation of CA1 neurons. Clinically, it has been shown that arginine-vasopressin may be involved in febrile convulsions. In the presence of enkephalin, IPSPs are diminished considerably and may be reversed. It appears that the change due to enkephalin is an increase of incoming potentials. Substance P produces membrane hyperexcitability causing depolarization and decreasing potassium conductance.

Considerable effort is being made toward understanding the nature and role of the GABA/benzodiazepine/ionophore receptor complex. This receptor complex plays an important role in conductance of the inhibitory chloride ion. GABA, a major inhibitory neurotransmitter, appears to exert its effects through an increased post-synaptic permeability to chloride ions. It now appears that there are several well-defined, independent but interacting binding sites contained in this membrane-bound complex; a binding site for benzodiazepine-like substances, ionophore binding sites, a GABA recognition site, and a barbiturate/picrotoxin binding site. It is postulated that these sites surround the chloride channel and activate or open the channel to allow an increase in chloride conductance. A number of drugs and chemicals can bind to each of these sites, with either agonist or antagonist activity. GABA-related depressants such as valproic acid, or GABA itself can bind to the GABA site increasing permeability of the inhibitory chloride ion. GABA related excitants such as bicuculline, pencillin or strychnine may bind to the GABA site to prevent chloride conductance. Barbiturates and many related antiepileptic drugs bind to the receptor complex and enhance GABA activity, while a number of chemicals, such as picrotoxin, or pentylenetetrazol prevent barbiturate binding and decrease inhibition.

Other investigators are examining indirect ways to increase GABA content. Drugs are being designed which will inhibit GABA-transaminase, the enzyme responsible for degradation of GABA, and drugs which enhance the activity of GAD, the enzyme responsible for production of GABA.

Other investigators have shown that GABA and benzodiazepines can modify the flux of calcium ions across cell membranes. Benzodiazepines have been found to inhibit a Ca^{++}-calmodulin stimulated protein kinase in brain membranes.

The relationship of the benzodiazepine/GABA/ion receptor complex and anticonvulsant drug mechanism of action is also under active investigation. Barbiturates increase GABA-mediated inhibition probably by enhancing GABA binding to the receptor, resulting in a decrease in presynaptic calcium entry. Phenobarbital thus appears to have a direct GABA-mimetic action; enhancement of GABA binding by phenobarbital results in an increase in the mean channel open time, with an increase in current and

enhanced inhibitory response. At high concentrations, phenobarbital shortens action potentials due to a decrease in calcium entry resulting in a decreased transmitter release. Since this effect occurs at concentrations higher than those required to prevent epileptiform discharges, this probably represents a sedative/hypnotic action. Phenytoin, on the other hand, appears to act on repetitive firing of neurons. Studies indicate that phenytoin acts on the sodium channel, resulting in an accumulation of sodium channels in the activated (open) state.

A small number of grants is devoted to the study and treatment of epilepsy in patients. Studies on surgical resection of the temporal lobe in patients with partial epilepsy continue with emphasis on the development of criteria for selection of patients and neuropsychological evaluation of patients following surgery. Two investigators are performing clinical trials in patients; one in infantile spasms and one in complex partial seizures. Other researchers are developing new methodology for detection prevention and treatment of seizures as well as assessment of the effects of seizures and their treatment on learning and behavior.

The Epilepsy Branch of the Neurological Disorders Program now supports a growing team of very talented young investigators. This team is composed of investigators whose aim is the elucidation of the basic mechanism of initiation of seizure discharges at cellular, tissue and organic levels. This information is being incorporated by other investigators in the areas of molecular pharmacology and medicinal chemistry in the design of exciting new antiepileptic drugs. Clinical investigators play a vital role with studies in humans which provide for improved patient care as well as feedback for basic scientists.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

SOUTHERN RESEARCH INSTITUTE (NO1-NS-0-2327)

Title: Studies of Toxicology and Selected Pharmacology of Potential Anticonvulsants

Contractor's Study Director: Robert G. Meeks, Ph.D.
Contractor's Study Supervisor: Keith Obrosky, Ph.D.

Date Contract Initiated: March 1, 1979

Current Annual Level: $513,000

Objectives:
1) Oral toxicity of candidate anticonvulsant compounds in beagle dogs and rat: This portion of the toxicity evaluation exposes potential toxicologic effect of candidate anticonvulsant compounds on a variety of organ systems in the dog (beagle) and rat. Initial 14 to 28-day studies are to establish a dose-range for the longer 91-day oral toxicity studies. Changes in body weight and food consumption are presumptive indices for a toxicological effect. A gross necropsy is performed at the end of study and any remarkable changes in tissues are examined. Various hematological and biochemical parameters are determined also. The results of the dose-range finding studies are transmitted to the NINCDS Project Officer within 21 working days following termination. The 91-day oral toxicity studies in either rat or dog (beagle) are larger in scope than the dose-range finding studies. Hematologic, biochemical, and urinary parameters are monitored several times. Histopathologic examination of tissue is carried out on all animals in order to evaluate cellular changes. A final written report of all aspects of these studies is completed within 100 days of completion of the study.
2) Synthesis of additional amounts of candidate compounds: The contractor shall synthesize and characterize additional amounts of test compounds for the toxicity studies as directed by the project officer. The number shall not exceed three per year when funds are available. The synthesis and characterization of the compounds must meet Good Laboratory Practices (GLP) requirements.

Methods Employed: Over 40 compounds which have completed the early pharmacologic evaluation of the anticonvulsant drug screening contract have been reviewed by the Subcommittee on Anticonvulsant Drugs during the last two years. The Committee has established priorities for the toxicologic evaluation of the compounds. Supplies of several compounds (2-5 kg) were requested from the supplier, received by NINCDS, and sent to the contractor. A study number was assigned to each compound and a protocol was written by the contractor describing in detail each aspect of the study. The contractor must then follow the approved protocol. Any deviations or changes must be approved by the Project Officer.

Significance to Biomedical Research and the Program of the Institute: The study data provided by this contract are vital and necessary to advance potential compounds through the Antiepileptic Drug Development Program in order that they might be used by patients with epilepsy. During the past year, two 13-week oral toxicity studies in rats were completed (ADD 40016, ADD 03055). In addition, three dose-range-finding studies were finished (ADD 40016, ADD 40037, ADD 03046).

Proposed Course of Contract: Four 13-week oral toxicity studies in rats have been scheduled (ADD 54001, ADD 03055, ADD 40037, ADD 09004). Two dose-range-finding studies are contemplated (ADD 17014, ADD 50016). The contract has the capability of doing two additional 13-week oral toxicity and four to five additional dose-range finding studies. The third year of the contract ends February 28, 1983, with a Technical Merit Review scheduled for October 1982.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

UNIVERSITY OF UTAH (NO1-NS-0-2335)

Title: Early Pharmacologic Evaluation of Anticonvulsant Drugs

Contractor's Project Director: Ewart A. Swinyard, Ph.D.

Date Contract Initiated: November 1, 1980

Current Annual Level: $548,000

Objective: To determine the anticonvulsant properties of novel organic compounds at various levels of testing from preliminary screening to extensive activity and toxicity profiles.

Methods Employed: Compounds are received by NINCDS from academic and industrial medicinal chemists and then are sent to the University of Utah for evaluation. The initial phase of the contract is to test all compounds for anticonvulsant and neurotoxic activity over a wide dose range. The median effective dose (ED_{50}) and the median toxic dose (TD_{50}) are determined for those compounds which possess significant activity in the initial evaluation. These parameters are determined at time of maximal pharmacologic activity following intraperitoneal administration. The compounds are evaluated for their ability to raise seizure threshold and/or prevent seizure spread. The data is analyzed and reviewed by the NINCDS staff and the results are transmitted to the suppliers of the compounds. Additional supplies of the most promising candidate compounds are obtained for advanced testing. A complete profile of acute neurotoxicity in mice following intraperitoneal administration of the candidate compound is determined, of which the median hypnotic dose (HD_{50}) and median lethal dose (LD_{50}) are included in the third phase of evaluation. The fourth phase includes the estimation of the median effective anticonvulsant dose and the median neurotoxic dose following oral administration. The fifth phase evaluates the median effective dose (ED_{50}) of candidate compounds for the ability to inhibit threshold seizures induced by bicuculline and picrotoxin and tonic seizures induced by strychnine. Phases 6 and 7 are carried out in rats. In Phase 6, the median effective anticonvulsant dose (ED_{50}) and the median neurotoxic dose (TD_{50}) are determined following oral administration. In Phase 7, the minimal lethal dose following chronic administration (five-day) is established along with its effect on anticonvulsant activity. The effect of candidate compounds on drug metabolizing has been included into Phase 7.

Significance to Biomedical Research and the Program of the Institute: This contract provides for the evaluation of the anticonvulsant activity and antiepileptic potential of new chemical compounds. For the year beginning October 1, 1981, 860 compounds were screened for Phase 1. Sixteen compounds have been completed through Phase 6 and seven through Phase 7. This work level exceeds that specified in the contract.

Proposed Course of Contract: The contract ends October 31, 1983, with a Technical Merit Review scheduled for summer 1983.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

UNIVERSITY OF MINNESOTA (NO1-NS-1-2371); UNIVERSITY OF VIRGINIA (NO1-NS-1-2367)

Title: Progabide in Partial Seizures

Contractors' Project Directors: University of Minnesota, Robert Gumnit, M.D. and Ilo Leppik, M.D.
University of Virginia, Fritz E. Dreifuss, M.D.

Date Contracts Initiated: September 30, 1981

Current Annual Level: $211,000 (University of Minnesota $126,000; University of Virginia $ 85,000)

Objectives: To characterize the efficacy and safety of a new GABA agonist, progabide, in the treatment of refractory partial seizures. To confirm the efficiency of the two-period crossover trial design in testing drug efficacy in partial seizures.

Methods Employed: The main study covered by these contracts is a randomized, double-blind, two-period crossover study comparing progabide with placebo when given as an add-on medication to patients with partial seizures refractory to therapy with two standard drugs, phenytoin and carbamazepine. Contracts have been let to two centers in order to recruit adequate numbers of patients. Methodology includes on-line analyses of plasma concentrations of the standard antiepileptic drugs and the investigational drug and its metabolites. Methodology also includes collection of individual patient data at each center site on micro-computers with recording of data on floppy disks programmed in advance at the Epilepsy Branch. The main study was preceded by a pilot study of four patients at each of the two centers.

Major Findings: The pilot study has been successfully completed. Five of the initial eight patients have reported some subjective improvement in their seizure disorder. In some patients, seizures which previously progressed to full complex partial seizures, with decreased levels of consciousness, now under the effect of the investigational drug appear to be experienced as simple partial seizures, without impairment of consciousness. Drug toxicity has manifested itself as dizziness and irritability of mood in approximately half of the patients in the pilot study. One patient suffered mild, transient cholestatic jaundice.

Significance to Biomedical Research and the Program of the Institute:
This study is intended to provide definitive evidence on the therapeutic potential of a new drug in the treatment of refractory partial seizures, the most important therapeutic problem in epilepsy. The study is important as a reinitiation of previous clinical drug efficacy studies, a major component of the Epilepsy Branch's Antiepileptic Drug Development Program. The study is also intended to promote methodological advances in the area of antiepileptic clinical drug testing.

Proposed Course: Contract is intended to provide for data on 30 completed patients by August 30, 1983 at the University of Minnesota and 30 completed patients by August 30, 1984 at the University of Virginia. Contracts are completed as of one month following the date of completion of the final patient.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

UNIVERSITY OF MINNESOTA (NO1-NS-80-2341)

Title: Epilepsy Information Transfer

Contractor's Project Director: Robert J. Gumnit, M.D.

Date Contract Initiated: 9/30/80

Current Annual Level: $208,674

Objectives: The objective of this contract is to transfer information being generated from the Minnesota Comprehensive Epilepsy Program to all appropriate audiences. The materials and information being developed for all phases of epilepsy in this research program need to be rapidly transmitted to improve treatment for people with seizures. The contractor is providing support and coordination to established clinical and laboratory research programs by virtue of interdisciplinary interchange through methods such as inhouse conferences. The contractor is training and educating physicians and other professionals in the newest advances in epilepsy research and treatment in an effort to specifically increase and quicken the flow of information from clinical research. The contractor is establishing a broad program for public education to help disseminate the newest advances in epilepsy treatment.

Methods Employed: This project began September 30, 1980. The contractor is developing, testing, and implementing a broad program for professional education for the purpose of demonstrating to physicians and other professionals the newest in advances in epilepsy research and treatment. All types of epilepsy and all age groups are included. Efforts are being made to develop, implement, and scientifically evaluate programs to train those who serve patients with seizures. The contractor is also developing, testing, and implementing a broad program of public education for the purpose of improving public and patient knowledge about epilepsy. Efforts are being made to develop, test and implement public education programs and materials in cooperation with appropriate lay organizations; develop, test and implement educational programs for the patient; and use methods for interdisciplinary exchange to provide support and coordination to established clinical and laboratory research programs.

Significance to Biomedical Research and the Program of the Institute: This program is designed to rapidly transfer information being developed from all phases of epilepsy research to individuals delivering health care services and to individuals and families of those with epilepsy. In addition, this contractor can obtain feedback information from individuals delivering health services and from consumers which may point the way to future areas of research.

Proposed Course of Contract: This project will continue until September 29, 1983.

Publications:

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Gumnit RG (Ed): Epilepsy. A Handbook for Physicians. Fourth Edition. University of Minnesota Press, Minneapolis, 1981, 64 pp.

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CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

Contractor	Title	Initiation Date	Project Director	Annual Level
MED COLL GEORGIA (NO1-NS-76-2340)	Comprehensive Epilepsy Program	6/30/76	D. Smith, M.D	$1,198,712
UNIV OF WASHINGTON (NO1-NS-76-2341)	Comprehensive Epilepsy Program	6/30/76	A. Ward, Jr., M.D.	1,140,764
UCLA (NO1-NS-80-2332)	Comprehensive Epilepsy Program	6/30/80	A. Delgado-Escueta, M.D.	1,267,580

Objectives: The objective of the Comprehensive Epilepsy Program is to facilitate applied research and to coordinate research and teaching with health care services related to persons with all types of epileptic seizures within a defined geographic area.

Methods Employed: Each contractor is conducting clinical and laboratory research in the diagnosis, treatment, prognosis and prevention of epilepsy. Each contractor is demonstrating to physicians and other professionals the newest advances in epilepsy research and treatment and is establishing a broad program for public education. In addition, each contractor is establishing the required procedures to assure, in a research setting, the availability to the person with epilepsy of complete and up-to-date preventive medical and rehabilitative psychological, vocational, educational, and social services.

Major Findings: All of the contractors showed evidence for the feasibility of establishing a program in their geographic area by a detailed description of clinical research capability, health care delivery capabilities, rehabilitation resources, etc., for the person with epilepsy. Clinical research projects encompass etiology, epidemiology, diagnosis, and treatment of epilepsy conducted in a multidisciplinary setting.

Significance to Biomedical Research and the Program of the Institute: Epilepsy is a significant national health problem. Despite recent advances, much remains to be learned about the causes and mechanisms of seizures in order to more effectively prevent, diagnose, and treat patients with seizures. These contracts are designed to increase the understanding of epilepsy by developing improved techniques for prevention, diagnosis, and treatment with the ultimate aim of substantially reducing the number of people who suffer from epilepsy and of controlling seizures to ameliorate their impact so that affected individuals may attain as much as possible a normal life. These studies, by studying an abnormal brain, may provide new insights into the normal functioning of the brain and may provide clues as to why the brain functions abnormally.

Proposed Course of Contract: Contracts NO1-NS-76-2340 and NO1-NS-76-2341 are scheduled to expire on 6/30/82. Contract NO1-NS-80-2332 will undergo peer review during FY 83.

Publications:

MEDICAL COLLEGE OF GEORGIA

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Nosek TM: How valproate and phenytoin affect the ionic conductances and active transport characteristics of the crayfish giant axon. Epilepsia 22:651-665, 1981.

Swift TR, Gross JA, Ward LC, Crout BO: Peripheral neuropathy in an epileptic population. Neurology (N.Y.) 31:826-831, 1981.

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CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

EXCERPTA MEDICA FOUNDATION (NO1-NS-3-2303)

Title: Publication of Epilepsy Abstracts, Volume 14

Contractor's Project Director: Pierre Vinken, M.D.

Date Contract Initiated: December 15, 1972

Current Annual Level: $55,000

Objectives: To scan serial publications and periodicals from approximately 3500 world biomedical journals and select appropriate articles to be included in Epilepsy Abstracts in accordance with the guidance of the Project Officer and his editorial advisors; prepare abstracts with appropriate translations into English from foreign languages; classify, index, and store the abstracts in a computer-retrievable form; and produce a 9-tract, 1600 bpi computer tape for use at NIH. The text is automatically set by computer-operated photocomposition. The Excerpta Medica Foundation produces camera-ready copy for each monthly issue of Epilepsy Abstracts, which includes an index of subjects and authors, and prints and distributes the journal monthly with a cumulative index at the end of the volume. In order to pay for the production of the camera-ready copy, printing, and distribution, the Excerpta Medica Foundation sells subscriptions to recover these costs.

Methods Employed: Subscriptions to Epilepsy Abstracts, each at annual cost of $77.00, have been acquired from interested persons by Excerpta Medica. Computer tapes were delivered to NIH bimonthly in accordance with the contract. These tapes comprise the EPILEPSYLINE data base retrievable throughout the country from B.R.S., Inc.

Proposed Course of Contract: The current contract expired in February 1982. Efforts are underway to secure another contract to insure the maintenance of the publication of Epilepsy Abstracts.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981--September 30, 1982

THE METHODIST HOSPTIAL (HOUSTON) - (NO1-NS-9-2321)

Title: Treatment of Infantile Spasms

Contractor's Project Director: Peter Kellaway, Ph.D.
Date Contract Initiated: September 30, 1979
Current Annual Level: $24,600

Objectives: To conduct a double-blind controlled crossover evaluation of corticotropin and prednisone in 25 patients with infantile spasms. Children who fail to respond to either treatment will be administered clonazepam in an open trial. Precise quantitation methods were developed in a predecessor contract.

Methods Employed: A request for proposals was issued in FY79 and resulted in the award of the present three year contract to The Methodist Hospital. After appropriate testing of the placebos, of corticotropin and prednisone, patients were admitted to this double-blind, two-period crossover trial. This clinical evaluation is a response-conditional crossover trial, i.e., patients who have 100% reduction in seizure frequency during the first treatment period are not crossed over to the alternative therapy.

Major Findings: Under the present contract the comparative efficacy of corticotropin and prednisone in infantile spasms was studied. As of this date, 20 patients have entered into the study; 16 patients have completed the protocol, 4 patients are currently in some phase of the protocol. One hundred and three (103) twenty-four hour monitoring sessions have been completed. In addition, eight infants have been monitored who did not prove to have spasms. Four patients responded to the initial drug, five patients responded to the crossover drug, and four did not respond to either treatment. Four patients entered the open clonazepam trial, none of whom responded. Five patients developed hypertension, a common side effect of corticotropin. One patient developed continuous herpes. All patients will complete the study by July 1982. A comparison of the three drugs--corticotropin, prednisone, and in failures, clonazepam--may be made when the study is unblinded and completed in July 1982.

Significance to Biomedical Research and the Program of the Institute: This contract will end with the completion of the 25 patients in July 1982. At this time, a definitive clinical statement can be made about the relative efficacy of corticotropin and prednisone in this severe disorder. The methodology employed to evaluate the treatment of infantile spasms (video recordings, EEG, and accellerometry) were adapted for use in another

multi-center trial. Hoffman-La Roche Inc. is supporting a clinical evaluation of nitrazepam in infantile spasms. Dr. Kellaway is serving as a consultant to that study; the Epilepsy Branch is cooperating in protocol development, data interpretation and analysis.

Proposed Course of Contract: The contract will end with the completion of 25 patients in July 1982.

Publication: Hrachovy, R.A., Frost, J.D., Jr., Kellaway, P., Zion, T., A controlled study of ACTH therapy in infantile spasms. Epilepsia 21:631-636, 1980.

UNIVERSITY OF KANSAS MEDICAL CENTER (NO1-NS-2-2313)

Title: Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis

Contractor's Project Director: Charles E. Brackett, M.D.
Date Contract Initiated: June 28, 1972
Current Annual Level: $58,000

Objectives: The main objective of the study was to determine the effectiveness of therapeutic treatment with phenytoin and phenobarbital in persons who suffer severe head injury and are thus liable to posttraumatic epilepsy. This study was preceded by a pilot study with prophylactic doses. The patients admitted to the severely injured protocol are being followed for an additional 18 months to provide information about the occurrence of "late" seizures.

Methods Employed: The current double-blind controlled clinical trial compared therapeutic doses of phenobarbital and phenytoin versus placebo. Patients were randomly assigned to either treatment group in each of two strata. The first stratum consisted of severe closed head injuries and the second consisted of severe dural penetrating injuries.

Major Findings: In the completed pilot study, 125 patients were accessioned to the protocol in which either phenobarbital, 60 mg, and phenytoin, 200 mg, or placebo were given to head injured patients daily for 18 months. These patients were then followed an additional 18 months. Eleven patients experienced seizures while on the study and four had seizures after completion of drug therapy. No significant difference in seizure incidence was found between the active and placebo groups on the low drug doses used.

The pilot study results led to the second phase of the contract work. Forty-nine patients were accessioned to the revised protocol in which patients randomized to active drug received higher, individualized therapeutic doses of phenytoin and phenobarbital for six months. Therapeutic range was achieved and maintained by frequent blood level analysis and dose adjustment. These patients were then followed an additional 12 months for seizure frequency. Ten patients experienced seizures while on the study (two, active; and eight, placebo). Analysis of the 49 patients in this series indicates that those patients with phenytoin and phenobarbital in therapeutic doses had a significantly lower incidence of posttraumatic epilepsy than those patients on placebo for the period of treatment.

Significance to Biomedical Research and the Program of the Institute: Using a conservative five percent incidence rate of posttraumatic epilepsy, the at-risk population of 500,000 serious injuries annually yields an annual incidence of posttraumatic epilepsy of 25,000 in the United States due to motor vehicle accidents alone. The Commission for the Control of Epilepsy and Its Consequences reported approximately $5,000 per person as a conservative but reasonable figure for the average cost to society and to the patient with epilepsy. Multiplying this by the annual incidence of posttraumatic epilepsy (25,000), an estimated $125,000,000 annually could be saved by the elimination of posttraumatic epilepsy subsequent to motor vehicle accidents alone. More importantly, the prevention of posttraumatic epilepsy in adults can relieve these individuals from the tremendous social, psychological as well as medical, burdens associated with the acquisition of a seizure disorder.

Proposed Course of Contract: The result of the pilot study and the treatment period are in publication. Because of the very protracted period of time during which posttraumatic epilepsy may occur, and the highly variable incidence of seizures occurring with the different types of severely head injured, the patients in the Phase II study are being followed for an additional 18 months. This follow-up will end in FY82. This additional information will provide for the collection of sufficient data to allow for inferences to be made regarding the occurrence of "late" seizures.

Publications: (1) Penry, J.K., White, B.G., Brackett, C.E., A controlled prospective study of the pharmacologic prophylaxis of posttraumatic epilepsy (abstract). Neurology (NY) 29:600-601, 1979.

(2) White, B.G., Pharmacological prophylaxis of posttraumatic epilepsy reconsidered. Epilepsia (In publication).

(3) White, B.G., Penry, J.K., Brackett, C.E., et al, Pharmacological prophylaxis of posttraumatic epilepsy. Prophylatic and therapeutic doses. Epilepsia (in publication).

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1981---September 30, 1982

UNIVERSITY OF WASHINGTON (NO1-NS-1-2349)

Title: Study of Experimental Anticonvulsant Drugs in Primates

Contractor's Project Director: Joan S. Lockard, Ph.D.
Date of Contract Initiated: February 16, 1981
Current Annual Level: $548,000

Objectives: To evaluate the anticonvulsant efficacy of drugs in primates with chronic partial seizures. Seizure frequency and behavioral toxicity are compared with drug dosage and drug blood concentration. Metabolic and pharmacokinetic studies are conducted prior to efficacy determination.

Methods Employed: A request for proposals was issued in FY80 and resulted in the award of the present three-year contract to the University of Washington. A series of studies were performed or being performed during the present year. These were assay and pharmacokinetic studies, efficacy studies, and metabolic studies involving three anticonvulsants. The results will provide the scientific basis for decisions regarding appropriate clinical trials.

Major Findings: Under the present contract the efficacy of progabide and pharmacokinetics of stiripentol were studied. Progabide seems to reduce seizure frequency by a small to moderate amount in the majority of animals. There is evidence of reduced seizure rates for considerable time after its withdrawal although this may be more related to the method of administration. The bioavailability of stiripentol appears to be limited by an extensive first pass effect. Kinetic behavior presents a prolonged terminal distribution phase. The drug is eliminated mostly by biotransformation with one-third of the dose found in the urine as a glucuronide.

Significance to Biomedical Research and the Program of the Institute: The availability of this model for selected drug candidates provides the potential scientific basis for decisions regarding appropriate clinical trials, thus conserving both time and funds as new drugs are developed. Such studies serve as an incentive to the pharmaceutical industry in developing new drugs.

Proposed Course of Contract: A change in the projected research includes the development of a model to evaluate the efficacy of a delivery system for insoluble, short half-life drugs. The development of such a model would expand the types of drugs that could be studied. The contract expires January 15, 1984, with a Technical Merit Review scheduled for July 1983.

Publications:

Lane EA, Levy RH: Metabolite to parent drug concentration ratio as a function of parent drug extraction ratio: cases of nonportal route of administration. J Pharmacokinet Biopharm 9(4): 489-496, 1981.

Patel IH, Levy RH: Intramuscular absorption of carbamazepine in rhesus monkeys. Epilepsia 21(1): 103-109, 1980.

Patel IH, Levy RH, Neal JM, Traser, WF: Simultaneous analysis of phenobarbital and p-hydroxyphenobarbital in biological fluids by GLC-chemical-ionization mass spectrometry. J Pharm Sci 69(10): 1218-1219, 1980.

Pastel IH, Wedlund P, Levy RH: Induction effect of phenobarbital on the carbamazepine to carbamazepine - 10, 11 - eposide pathway in rhesus monkeys. J Pharmacol Exp Ther 217(3): 555-558.

Stella VJ, Yamaoka K, Levy RH: An added complication in the estimation of apparent hepatic blood flow in vivo by pharmacokinetic parameters. Drug Metab Dispos 9(2): 172-173, 1981.

Viswanathan CT, Levy RH: Plasma protein binding interaction between valproic and salicylic acids in rhesus monkeys. J Pharm Sci 70(11): 1279-1281, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-02511-02 EB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Analytical Methods of Analysis for Potential Anticonvulsants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS
Others:	Wayne Yonekawa	Pharmacologist	EB NDP NINCDS
	Jill Shaw	Medical Technician	EB NDP NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analytical methods for the quantitation of drugs are needed for the various phases of drug development. These methods must have specificity and sensitivity to quantitate drugs in dosage forms of the toxicology study, and in body fluids for human pharmacokinetic and efficacy studies. Chromatographic methods are most useful for this purpose. Drugs are extracted. The physical and chemical characteristics of each compound is evaluated in order to determine the suitable chromatography and detection. Volatile compounds are subjected to gas-liquid chromatography (GLC). Polar compounds are quantitated by high pressure liquid chromatography (HPLC). Extraction procedures for a variety of compounds were developed using a preferential solvents systems theory. The final methods were found to be suitable for a variety of both animals and humans.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1-NS-02512-02 EB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Inhibition of Microsomal Primidone Metabolism by Phenytoin

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Maria G. Porro	Pharmacologist	EB NDP NINCDS
Others:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Phenytoin has been reported to cause an elevation of plasma phenobarbital in epileptic patients. Phenytoin has been shown in patients to 1) stimulate the metabolism of primidone to phenobarbital and 2) inhibit the hydroxylation of phenobarbital. The concomitant rise in phenobarbital levels can cause sedation in epileptic patients. The use of an in vitro system of hepatic microsomes can be of benefit in elucidating the mechanism of this drug-drug interaction. Microsomes will be obtained from adult male phenobarbital-treated Holtzman rats. The rate of phenobarbital production from primidone and the hydroxylation of phenobarbital will be followed at 37°C in a NADPH and NADP system. The Michaelis constant (K_m) Maximal Velocity (V_{max}) will be determined for the conversion of primidone to phenobarbital and for the conversion of phenobarbital to hydroxyphenobarbital. The inhibition constant (K_I) will be determined for phenytoin in this system.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-NS-02539-01 EB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

HPLC Analysis for ADD 67003 (Progabide) and Its Major Metabolite in Plasma of Epileptic Patients

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Wayne Yonekawa	Pharmacologist	EB NDP NINCDS
Others:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.75	0.75	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Progabide (ADD 67003) has been shown to be an effective anticonvulsant in various animal models of epilepsy. It is metabolized to 4-[(4-chlorophenyl)(5-fluoro-2-hydroxy phenyl)methylene] butanoic acid. This acid metabolite has anticonvulsant activity similar to that of Progabide. Progabide is now undergoing a NINCDS-sponsored clinical efficacy trial. Plasma level measurements of both parent drug and active metabolite are an integral part of these studies. A high pressure liquid chromatographic (HPLC) method has been developed that is sensitive enough to simultaneously quantitate both drug and metabolite in plasma of epileptic patients receiving orally administered drug. This method uses an electrochemical detector for specificity and sensitivity. Both drug and metabolite can be quantitated to levels of 10 ng/ml of plasma and the assay is presently being used in the NINCDS clinical studies.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1-NS-02540-01 EB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

In Vitro Inhibition of Phenytoin Metabolism by Carbamazepine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS
Others:	Wayne Yonekawa	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Carbamazepine has been shown to increase plasma phenytoin levels in epileptic patients receiving both drugs. The rise in phenytoin plasma levels can lead to nystagmus, sedation, and other central nervous system side effects. The use of an in vitro system of hepatic microsomes can be used in elucidating the biochemical mechanism of this drug interaction. Microsomes will be obtained from rats, mice, and rabbits. The Michaelis-Menton (K_m) and maximal velocity (V_{max}) will be determined for each species by following the rate of formation of HPPH, the major metabolite of phenytoin. This enzymatic process will be followed at 37°C in a NADPH-NADP system. The species which appears to have a similar K_m, V_{max} and metabolic profile to humans will be used for this study. The type of inhibition (competitive, noncompetitive) and the inhibition constant (K_I) for carbamazepine will then be determined.

PHS-6040
(Rev. 2-81)

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Developmental Neurology Branch, NDP
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Table of Contents (cont'd)

ANNUAL REPORT
For Period October 1, 1981 through September 30, 1982
Developmental Neurology Branch, Neurological Disorders Program
National Institute of Neurological and Communicative
Disorders and Stroke
National Institutes of Health

GENERAL SUMMARY

I. OVERVIEW

The Developmental Neurology Branch (DNB) develops and implements a program of research on the neurobiological aspects of the developmental disorders of children including cerebral palsy and other motor disorders, autism and behavioral disorders, mental retardation and learning disorders, and central nervous system birth defects and genetic disorders. The DNB is formally organized into sections which correspond to these four subprogram areas. During this year the DNB administered about 195 grants classified as Disorders of Early Life, a major disorder category within the extramural grant program.

New initiatives through program announcements have been issued by the DNB in Reye's syndrome, neonatal brain disorders, neural tube defects, and neurophysiology of learning disorders. A new contract study designed to measure the possible effects of phenobarbital therapy on the cognitive and neurological status of the treated child who has experienced febrile seizures has been awarded.

The DNB has continued a major effort during this fiscal year to meet the objectives of the Comprehensive Plan for Analysis and Interpretation of NINCDS Collaborative Perinatal Project (NCPP) Data. A major area of the Comprehensive Plan was completed during the year: a book dealing with neuropathology is in press. Also, during the year a total of 53 papers were published or are in press; these papers are cited in the body of the report. As the NINCDS will soon complete its use of the Collaborative Perinatal Project data, an RFP has been issued which requests proposals for the production of a "Users Guide" to the NCPP data to facilitate the long-term management of the microfilm and computer tape files as a national data resource by the National Archives. The awarding of this contract is anticipated in this fiscal year.

Other activities of the DNB include primary responsibility for administering the Privacy Act within the NINCDS and conducting reviews of NINCDS research contract proposals to assure the protection of human subjects.

II. REYE'S SYNDROME INITIATIVE

A program announcement on Reye's syndrome was sponsored by NINCDS and published on May 16, 1980 which requested individual and program project

research grant applications. This program announcement was cosponsored by three other Institutes. There have been six grants funded by NINCDS under this program announcement. One, a large program project, is investigating in Reye's syndrome cerebral circulation, metabolism, and electrophysiology; cerebral ammonia metabolism; lipid metabolism and hepatic energy states; virologic and immunologic problems; and developing an animal model. Other new grants are investigating metabolic coma and cerebral energy metabolism, mitochrondial function, metabolic patterns during disease; and muscle metabolism after recovery.

The DNB served as the focal point within the NINCDS in the planning of a Consensus Development Conference on the Diagnosis and Treatment of Reye's Syndrome which was held on March 2-4, 1981. The Consensus Conference focused on the criteria for diagnosis and on the treatments in use, with particular attention to the treatment of the syndrome as a function of the severity of the syndrome. The Consensus Statement was published in the Journal of the American Medical Association, November 27, 1981.

III. SECTION REPORTS

Section on Cerebral Palsy and other Motor Disorders

A program announcement was published on January 2, 1981 which requested program project grant applications on clinical research on neonatal brain disorders focusing on the pathogenesis, diagnosis, treatment, and outcome of intraventricular hemorrhage in low birthweight neonates, hypoxic-ischemic encephalopathy in full-term infants, neonatal seizures, and metabolic disorders relevant to neonatal brain function. Six program project applications were received, but none were funded. Amended applications are expected.

Current activities on febrile seizures include several invited presentations and chapters for books. An NIH Consensus Development Conference on Long-term Management of Children with Febrile Seizures was held in 1980. Results of the consensus meeting have been published in lay and professional journals, and the papers have been edited for a monograph, published in 1981. Results of the meeting are available in a DHHS publication Febrile Seizures, a National Institutes of Health Consensus Development Conference Summary, Vol. 3, No. 2.

The effect of anticonvulsant medication, particularly phenobarbital, on the developing nervous system has been a major concern of the DNB. The Consensus Conference on Febrile Seizures also emphasized this concern, and a contract has been awarded which will study development of cognitive and neurological function relative to long-term phenobarbital therapy in children who have experienced febrile seizures. A Request for Contract Proposal (RFP) was issued on March 13, 1981 entitled "Behavioral and Cognitive Side Effects of Phenobarbital Used for Prevention of Febrile Seizure Recurrence," and an award was made to the University of Washington, Seattle, on May 1, 1982.

A study of the EEG as a predictor of febrile seizures has begun in Yugoslavia in pursuance of another of the recommendations. The Section has also

participated in establishment of a group to investigate time trends in CP incidence in the United States in an effort to assess the results of changes in newborn care in this country.

In the cerebral palsy analysis of NCPP data, a univariate screen has been performed to evaluate maternal and pediatric conditions most strongly associated with cerebral palsy. Four of five regression analyses have been run. Cerebral palsy at 7 years is found more frequently in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma. Clearly handicapping cerebral palsy was present at age 7 in 22-33/10,000 children, the range being related to race and sex. Studies have been completed and published demonstrating the relationship of birthweight and gestational age to cerebral palsy, and the relationship of physical findings in the newborn period, at four months, and at one year, to chronic motor handicap.

Another published study concerns low Apgar scores as predictors of long-term morbidity. Associated handicaps have been investigated in children with cerebral palsy, and natural history described in children who "outgrew" cerebral palsy, i.e., those children who showed signs of cerebral palsy at an earlier age but at the 7-year examination were free of motor handicap. The major multivariate analyses relating to the antecedents of cerebral palsy are now in progress. Several analyses are underway to clarify associations revealed in the regression analyses.

In the convulsive disorders analysis of NCPP data, major findings are that approximately one in 20 children (57/1000) at age seven years have had at least one seizure. About 1/10 of that number (4.8/1000) had active epilepsy by the age of seven. In the NCPP population, epilepsy in childhood is approximately equal in prevalence in blacks and whites. Two-thirds of children who had seizures between one month and seven years of age had febrile seizures only. Data on prevalence of specific seizure disorders in early childhood are now available and were presented at an international meeting on child neurology. Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap -- either mental retardation or cerebral palsy, or both. Seizures occurring in the first months of life were associated with a relatively high rate of death or subsequent disability including cerebral palsy. Neonatal seizures were found to be a major marker of risk for subsequent neurologic morbidity, and neonatal seizures in full term infants with very low Apgar scores appeared to be an important predictor of chronic neurological disability. Predictors of neonatal seizures are under investigation. A manuscript on neonatal seizures in the NCPP has been prepared under contract, and is in press. Low birthweight, short gestation, and low Apgar scores were not important risk factors for seizure disorders in children who did not also have cerebral palsy. The major multivariate analyses concerning the antecedents of convulsive disorders are now in progress. Mothers with noneclamptic seizure disorders have been reported by others to be at increased risk for certain problems in their pregnancies or progeny. These associations and possible intermediary factors have been explored in the population of the NCPP, and a paper on this topic is in press.

A study of febrile seizures has been a major focus of the convulsive disorders area. Of 1706 children with febrile seizures followed to the age of 7 years, 2% had become epileptic by the age of 7 and another 1% had had at least one nonfebrile seizure not meeting the definition of epilepsy. Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ or increased vulnerability to learning disorders. Three risk factors were identified which served to mark children at special risk of subsequent epilepsy among children who have had febrile seizures. The best predictor of recurrence of febrile seizures was early age of onset.

Section on Mental Retardation and Learning Disorders

A program announcement encouraging the submission of research grant applications on brain neurophysiology and/or neurochemistry in learning disorders, and related research supporting this effort, was published on January 1, 1982. Of particular interest are studies using evoked potential and EEG measures. Other areas of interest include neuroendocrine, metabolic and neuroradiological studies. The two primary goals are: (1) to develop objective and reproducible diagnostic criteria for identifying homogeneous subgroups of children with learning disorders; (2) to refine neurophysiological techniques for evaluating cortical functions in these LD subgroups and in normal comparison groups. The reliability and validity of measures of brain electrical activity need to be investigated in both study and normal control groups by age, sex, type of learning task, and hemispheric specialization. Research should be directed at developing knowledge of the neurophysiology of learning disorders, and expanding the capability for accurate diagnosis. This research would require a multidisciplinary approach involving participation from such areas as neurophysiology, developmental neuropsychology and pediatric neurology. Approximately 100 inquiries and requests for additional information have been received from members of the research community.

The Section has participated in the scientific meetings of the Association for Children with Learning Disabilities, the American Psychological Association, and the Child Development Research Group. The Section also participated in the meetings of the American Psychological Association and the Behavior Genetics Association.

In the mental retardation analysis of NCPP data, tabular displays of the data have been completed, and a monograph reporting on 37,000 children is in preparation. Risk factors were examined separately for severely and mildly retarded children, and for subgroups without an identified cause or major neurological abnormality. The incidence of mild retardation (1% in whites and 5% in blacks) and to a lesser degree, of severe retardation (0.5%) was inversely related to socioeconomic status. Among the severely retarded, 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded group as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroups of severely retarded with unknown etiology, perinatal risk factors include non-CNS mal-

formations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. Special studies of drugs taken during pregnancy and of the incidence of mental retardation in relatives were conducted.

In the learning disorders area, a monograph has been reviewed for publication and a revised version is in preparation. The findings show that among children with at least average IQ scores but below average achievement test scores, socioeconomic status and family size were better predictors of unexpected school failure than were indices of physical or neurological status. Beginning in the preschool period, low achievers had higher frequencies of cognitive and behavioral problems, and neurological soft signs than did their IQ-matched controls. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in the predictors as well as in the incidence of unexpected academic failure. A summary of results is being published in a chapter on the methods and findings of the Collaborative Perinatal Project to be included in a book on longitudinal research in the United States.

Analyses in the area of obstetric medication and later physical and cognitive development in a cohort of normal births are completed and a report is in preparation. The findings suggest that inhalants are independently associated with deficits in psychomotor functioning in infancy, and that some drugs given during labor and delivery are associated with lower scores on cognitive tasks at later ages.

The final report of the study of symptoms of minimal brain dysfunction has been published (Nichols, P.L., and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study, Erlbaum, 1981).

Section on Birth Defects and Genetic Disorders

A program announcement was published on neural tube defects on December 12, 1981. The research goals of this program are the attainment of knowledge and understanding about normal and abnormal neural tube formation, specific etiologies of neural tube defects, the mechanisms which these etiologies initiate, the molecular and gross events which lead to neural tube defects, individual and population differences in incidence and in susceptibility to the forces which produce neural tube defects, and the nature of such susceptibility; and the utilization of this knowledge to develop measures for the prevention and treatment of neural tube defects. The scope of this program encompasses research in developmental aspects, natural history, and prevention of neural tube defects, utilizing a variety of subjects, approaches and methods.

The Section has been responsible for the administration of some 90 research grants mainly in the areas of developmental neurology and genetic disorders of lipid metabolism. Among other activities is a compilation of a comprehensive list of all known heritable disorders of the nervous system which to date numbers about 900.

The Section Chief took an active part in the 9th World Federation of Neurology Workshop on Huntington's Chorea, participated as an invited speaker

in the 9th International Congress of Neuropathology, lectured to medical students at George Washington University as an Associate Clinical Professor of Neurology, and to various other scientific and lay groups. He also participated in the NIH Interinstitute Medical Genetic Conferences and engaged in genetic counseling.

Two parts of the 11-part program plan for the comprehensive analysis of NCPP data in the area of congenital malformations remain to be completed: the analysis of minor and multiple malformations, and the analysis of the 7-year malformations. The analysis of minor and multiple malformations has been designed, input variables have been selected and defined, and preliminary tabulations have been produced. The analysis of the 7-year malformations updates the malformation finding in a cohort of children originally followed through the first year of life. Of those alive at 1 year 77.8% were examined at 7 years, and a further 14.7% were followed for some time from 1 to 7 years, though they were not examined at 7 years. Only 7.5% were completely lost to study. Findings from the analysis of 7-year malformations indicate that the proportion of children with malformations at 7 years is higher than that at 1 year mainly due to newly identified eye, mouth and genitourinary malformations and tumors. A large number of verifications and corrections has been undertaken before final tabulations are made.

Epidemiologic analysis of neural tube defects has shown that increased risk for these defects is associated with diabetes mellitus and organic heart disease in the mother, diuretics, antihistamines, sulfonamides and thyroxin taken during the first trimester, and short immediately previous pregancy interval. The last finding supports the hypothesis of fetus-fetus interaction as an etiologic factor in the occurrence of neural tube defects.

Studies of twins are in progress to assess and interpret the influence of maternal socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of NCPP twins.

Section on Autism and Related Behavioral Disorders

A new chief for the Section on Autism and Related Behavioral Disorders, Martha Bridge Denckla, M.D., assumed duties on December 28, 1981. A series of meetings with counterpart extramural program administrators from NIMH and NICHD have advanced and focussed the NINCDS-DNB specific mandate to investigate the neurobiologic basis of autism and related behavioral disorders. With NIMH representatives, the Section Chief co-founded a Child Development Research Study Group, inviting interested professionals from NINCDS-DNB, NICHD and NIMH to attend monthly meetings. At the monthly meetings, the specific research activities and interests of each of the twenty participants are shared. Discussion of common research concerns has led to plans for collaborative initiatives and program announcements. Research liaison-collaboration with the intramural unit on Childhood Mental Illness has been established (e.g., planning studies of evoked potentials

and cerebral blood flow in autistic, learning-disabled, and normal children). The Section Chief met with the National Society for Autistic Children Board of Directors and Medical Advisory Board chairman on March 4, 1982, and gave an address on "Research Initiatives on Autism" on July 6, 1982 at the NSAC national conference in Omaha, Nebraska.

Collaborative Perinatal Section

The Unit for Data Collection is responsible for maintaining the NINCDS Collaborative Project files in accordance with a system designed to facilitate data retrieval. During the fiscal year major efforts were concentrated on editing the NCPP microfilm, setting up the completed microfilm file, supplying data to DNB professional staff, outside investigators and consultants, providing research assistance to on-going studies, and preparing NINCDS microfilmed records for Federal Storage. Approximately 27,000 records are now at the Federal Records Center and the balance of the NCPP file, approximately 32,000 records, are awaiting pick-up for delivery to the Federal Records Center. The master copy of the NCPP microfilm and the computer tape files will be transferred to National Underground Storage Inc. in Bayers, Pa. An RFP for creation of a "Users Guide" was issued and a contract award is anticipated in this fiscal year. Research assistance via computer tapes, computer printouts or microfilm was provided to 20 investigators (8 in-house and 12 outside investigators).

The Unit for Production of Data Analysis has as its basic mission the processing and storage by digital computer of the medical research data collected by the NCPP. All research files have been completed. A financial system that audits all computer funds spent by the Branch and an automated bibliography of all NCPP publications are now operational.

IV. ADDITIONAL ACTIVITIES

The Office of the Chief, DNB, continues as the NINCDS focal point for implementation of the Privacy Act. The Chief, DNB, continues to serve as NINCDS Privacy Act Coordinator. Activities for this fiscal year include the following: (1) advice to NINCDS personnel regarding Privacy matters; (2) determination of the applicability of the Privacy Act to each new NINCDS contract involving human subjects; (3) required annual report prepared and submitted to the NIH Privacy Act Coordinator; (4) reviewing requests for access to or amendment of grant records; (5) attending orientation sessions regarding changing regulations in implementation of the Act; and (6) revising NINCDS System Notices to comply with new regulations.

The Office of the Chief, DNB, continues to administer the Clinical Research Panel, NINCDS Contract Review for the Protection of Human Subjects, and the Chief, DNB, serves as Chairman. This panel has the responsibility for reviewing NINCDS contracts for adherence to DHHS and NIH rules and regulations regarding the protection of human subjects in research and recommending approval or disapproval to the Director, NINCDS.

UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON (NO1-NS-2-2395)

Title: Behavioral and Cognitive Side Effects of Phenobarbital Used for Prevention of Febrile Seizure Recurrence

Contractor's Project Director: Jacqueline R. Farwell, M.D.

Current Annual Level: $183,992.00

Objectives: The University of Washington will conduct a randomized, placebo-controlled study to determine the effects of long-term phenobarbital treatment in children aged one to five years who have had febrile convulsions. The primary objective is to assess the effects over a two-year period of treatment, and six months after treatment termination, of phenobarbital on behavior and cognitive function. A secondary objective is to evaluate the effects of febrile seizure recurrence on behavior and cognitive function, and to compare these with the effects of prophylactic treatment.

Significance to the Program: This contract results from recommendations of the NINCDS Consensus Panel on Febrile Seizures. Febrile seizures are a common occurrence in early childhood, and uncertainty exists whether the benefits of treatment for prevention of recurrence outweigh its risks. In addition, phenobarbital is the most commonly used anticonvulsant in infancy and childhood, and information on its behavioral and cognitive side effects on the developing child will be of great value in other neurologic disorders.

Course of Contract: May 1, 1982 through April 30, 1985. (A TMR will take place before the two final years.)

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1981 through September 30, 1982

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS (N01-NS-3-2312)

Title: Combined Neuropathologic and Epidemiologic Study

Contractor's Project Director: Floyd H. Gilles, M.D.

Current Annual Level: $ 0.00

Objectives: The contract has analyzed the neuropathology collection of the NINCDS Collaborative Perinatal Project (NCPP). An estimate of the quality of the material and a catalogue of gross brain abnormalities has been prepared. Plots of fetal brain weight of grossly normal brains against estimated gestational age, utilizing a Gompertz function, were made and an analysis completed relating events of pregnancy, labor, and delivery. A comparison was made of rate of brain weight acquisition in utero to rate of brain weight acquisition after birth as a function of total (gestational plus survival) age. A study was made of intracranial hemorrhage including topography of hemorrhage. Risk factors associated with perinatal telencephalic leucoencephalopathy were studied. A cerebral necrosis study included criteria of necrosis in the perinatal brain, and an evalution of selected risk factors in relation to subclassification of neuronal and white matter necrosis.

Major Findings: Review and classification of pathology material are complete. Data analysis is complete and a 27-chapter monograph has been completed, reviewed, and approved for publication.

Course of Contract: June 1, 1973 through December 31, 1976. The contract is terminated; and the monograph is being published.

Publications: Gilles, F.H., Leviton, A., and Dooling, E.C.: Developing Human Brain: Growth and Epidemiologic Neuropathology. Littleton MA: Wright-PSG (in press).

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1981 through September 30, 1982

UNIVERSITY OF MICHIGAN (NO1 NS 5-2308)

TITLE: Physical Growth Analysis

Contractor's Project Director: Stanley M. Garn, Ph.D.

Current Annual Level: $ 00.00

Objectives: To develop the physical growth measurement data on the 50,000 children examined within the framework of the NINCDS Collaborative Perinatal Project (NCPP). Specifically:

1. Develop for body weight, length, chest circumference and head circumference, a set of tabular, percentile, normative tables of (a) size-for-age, (b) increments of size for age-interval, (c) size-for-size for age and size for gestation length for whites, blacks and Puerto Ricans separately and for boys and girls separately. This set of tables is largely intended as a reference document for the NINCDS Collaborative Perinatal Project.

2. Develop a set of summary tabulations and reports, directed to the major pediatric and growth-related users, complete with narrative and graphs, with the purpose of providing in the professional literature both an account of major substantive findings, and an in-the-literature account of the major data.

3. To correlate the incidence and prevalence of dental and facial abnormalities with neurological defects, congenital abnormalities and other disorders of childhood.

Major Findings: The tables, with accompanying graphs, as outlined in 1., above, are complete. Findings are reflected in approximately 27 publications to date.

Significance to the Program: The findings are important to the pediatric community as well as to physical anthropologists and nutritionists in that they represent results from the largest longitudinal data base yet studied in the U.S.

Course of Contract: Terminated April 30, 1980. Dr. Garn continues to analyze and publish NCPP data with support from sources other than the NINCDS. The planned series of publications is being completed and a final, comprehensive report has been requested.

Publications:

Garn, S.M., Ryan, A.S., and Abraham, S.: New values defining "low" and "deficient" hemoglobin levels for white children and adults. Ecol. of Food and Nutr.: 11:71-74, 1981.

Garn, S.M.: Noninvasive measurements of bone mass and their clinical applications. Ecol. of Food & Nutr: 10:195-197, 1981.

Garn, S.M.: Aging Students? Physical Anthropology News: 1(1):9-10, 1981.

Garn, S.M., Ryan, A.S., Owen, G.M., and Falkner, R.: Developmental differences in the triceps and subscapular fatfolds during adolescence in boys and girls. Ecol. of Food & Nutr.: 11:49-51, 1981.

Garn, S.M.: The growth of growth. Am. J. Phys. Anthropol: 57(2):191, 1982.

Garn, S.M., Ryan, A.S., and Higgins, M.W.: Abstract: Implications of fatness and leanness. Am. J. Phys. Anthropol.: 57(2):191, 1982.

Garn, S.M., Johnston, M., Ridella, S., and Petzold, A.S.: In reply: to Dr. Cunningham and smoking and pregnancy. Am. J. Dis. Child.: 136:82, 1982.

Garn, S.M.: Review: Radiology of the pediatric elbow. Radiology: 142:366, 1982.

Lamb, M.E., Garn, S.M., and Keating, M.T.: Correlations between sociability and motor performance scores in 8-month-olds. Infant Behavior and Development: 5:97-101, 1982.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1981 through September 30, 1982

THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA. (NO1-NS-7-2376)

Title: Analysis of General and Placental Pathology Data

Contractor's Project Director: Richard L. Naeye, M.D.

Current Annual level: $ 0.00

Objectives: The objectives of the last extension of the contract were (1) to complete the determination of the effects of smoking on the fetus, (2) a further explanation of the relationship between prepregnancy weight for height and placental growth as related to fetal growth and pregnancy outcome, and (3) a determination if selected factors thus far examined have an independent influence on long term psychomotor development in NCPP children.

Major Findings: Findings are reflected in approximately 44 publications to date.

Course of Contract: The contract terminated July 31, 1979; extra time is allowed to complete the planned series of publications, and a final, comprehensive, report is expected. Dr. Naeye continues to analyze and publish NCPP data with support from an NINCDS grant (1 RO1 NS 16403-01).

Publications:

Naeye, R.L.: Coitus and antepartum haemorrhage. Br. J. Obstet. Gynaecol.: 88: 765-770, 1981.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1981 through September 30, 1982

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS: (N01-NS-7-2377)

TITLE: A Prospective Cohort Epidemiologic Study of Learning Handicaps in Children Attending School

Contractor's Project Director: Alan Leviton, M.D.

Current Annual Level: None

Objectives: Conduct analyses of antecedents of school behavior and school achievement at age 9 in an identified sample of children in the Boston component of the NINCDS Collaborative Perinatal Project (NCPP) for the purpose of identifying risk factors for learning disorders.

Major Findings : Five learning handicaps in boys and six in girls have been identified as outcomes of interest. Antecedents are being analysed by epoch--e.g.-- pre-pregnancy, pregnancy, delivery, early postnatal. An interactive multiple logistic regression procedure is being used to analyse the data. Risk factors for learning handicaps include low family income, large family size, prior abortions, and some complications of pregnancy.

Course of Contract: The contract which began on September 30,1977 terminated November 14, 1980. Additional time has been allowed for completion of a monograph. Although progress has been slowed because of the consulting statistician's move to Dartmouth, the Project Director estimates that the monograph should be completed before the end of calendar 1982.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1981 through September 30, 1982

BETH ISRAEL HOSPITAL, BOSTON, MASSACHUSETTS (N01-NS-8-2381)

Title: Comprehensive Study of Labor and Delivery Effects on Offspring

Contractor's Project Director: Emanuel A. Friedman, M.D.

Current Annual Level: $0.00

Objectives: The objectives are (1) to determine the effects on the fetus and the surviving infant of clinically definable labor factors, labor disorders and the spectrum of delivery procedures, and thus to identify and quantitate the specific risk factors in labor and delivery that contribute to perinatal mortality and to the development of long-term neurological and developmental disorders in children, and (2) to determine relationships between the various types of maternal anesthesia-analgesia and development of the child; specifically, to examine in detail the time-dose relationships and drugs used in combination during the course of labor and delivery, in relation to long-term neurological outcome in the child.

Major Findings: Work on the contract has progressed and the required report following Phase 9 has been received. The monograph is now being written.

The contractual requirements for the ninth phase of this contract include completion of all foregoing efforts so as to define the high-risk labor and delivery constellations, and to proceed further by categorizing possible predictor variables in the maternal background so as to characterize the gravida-at-risk.

All data from the original index population (vaginal delivery with fully defined labor progression pattern) have now been integrated with data from the distinctive subgroups made up of patients delivered by cesarean section and those who delivered stillborn infants.

Stratified by parity, there were 2,642 nulliparas and 3,261 multiparas. When examined by the level of cervical dilatation that had been achieved at the time the arrest occurred, nulliparas averaged 6.48 cm. (standard deviation 1.76, standard error 0.03, modal value 5.0 cm.); multiparas averaged 6.60 cm. (standard deviation 1.70, standard error 0.03, modal value 8.0 cm.). In the course of examining the distribution of data according to the level of dilatation, we encountered the now-familiar zero end-digit clustering phenomenon that we have come to expect in these analytic studies. Arrest prior to 4 cm. is a rarity (192 cases or 1.06 percent of the index population and 3.25 percent of all documented arrest cases). Moreover, the frequency remains at rather a constant level regardless of the degree of dilatation at which the arrest occurred beyond this point (averaging 15.2 percent for each centimeter increment subgroup from 4 to 9 cm.).

The distribution of levels of dilatation at which arrest occurred has been stratified by parity. In general terms, multiparas arrested labor at more advanced cervical dilatation than nulliparas, but the range was broad in both subgroups. Of greater interest in this regard was the duration of the arrest according to the level of dilatation achieved. In nulliparas, for example, the mean duration was 1.57 hour (standard deviation 0.34, standard error 0.01 hour), as contrasted to the much shorter average period of arrest in multiparas of 0.93 hour (standard deviation 0.55, standard error 0.01 hour).

This was further elaborated by the level of dilatation to show that the duration of arrest "tolerated" by the physicians managing the patient was in general much longer at lower dilatations than at more advanced dilatations by a factor of more than 2.5 times in nulliparas and more than 6.5 times in multiparas. This is illustrated by a 3.02 hours of arrest in nulliparas at 3.0 cm. of dilatation versus 1.17 hour of arrest at 9.0 cm. dilatation (2.58-fold difference); at the same levels of dilatation in multiparas, the durations of arrest were 3.71 and 0.57 hour, respectively (a 6.51-fold difference).

We may conclude from these data and the preceding observations relating to outcome that arrests of short duration are innocuous both with regard to delivery prognosis and fetal/infant prognosis. This is reflected in the low neonatal and perinatal mortality data as well as the rare cesarea section performed among them. The data also permit us to conclude, with considerable reliance, that prolonged durations of arrest at any level of cervical dilatation is ominous with regard to both the probability of cesarean section and the likelihood of a bad outcome for the infant.

Course of Contract: March 13, 1978 through September 12, 1982. A six-month extension has been approved for preparation of the monograph.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02058-10 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Convulsive Disorders Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS
PI:	D.G. Hirtz	Expert Consultant	DNB NINCDS

COOPERATING UNITS (if any)
Dr. J. Freeman, Johns Hopkins
Dr. K. Holden, Johns Hopkins
OBFS, OD, NINCDS

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.6	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study examines the relationship between perinatal factors and the occurrence of seizure disorders in childhood in a large, prospectively studied population. In addition to the central question of etiology, it investigates frequency, prognosis, demographic characteristics, and a number of other aspects of these disorders. Univariate screen of maternal, obstetric, and pediatric risk factors, and demographic analysis, have been completed. File creation for multivariate analysis is now complete, and regression analyses are in progress. Selected topics of particular clinical relevance are under examination.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02059-10 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Cerebral Palsy Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: K. B. Nelson	Pediatric Neurologist	DNB NINCDS
PI: J. H. Ellenberg	Mathematical Statistician	OBFS NINCDS

COOPERATING UNITS (if any)
OBFS, OD, NINCDS

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH; Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.8	0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This large prospective study attempts to add to available knowledge of the perinatal factors associated with motor handicaps in childhood, the primary goal being to identify areas for possible preventive efforts.

Studies on the prevalence, on perinatal factors and neonatal signs in the early recognition of cerebral palsy have been published. Data on demographic analysis and a univariate screen of maternal and pediatric factors associated with cerebral palsy are available. Studies on early recognition of cerebral palsy, and on natural history of children with early motor abnormalities, have been published. Multivariate analysis is nearing completion.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02060-10 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Birthweight-Gestational Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Drage Chief DNB, NINCDS

COOPERATING UNITS (if any)

J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.10	0.05	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The final analyses, including a rerun of parts of Phase II and all of Phase III have been completed. Phase II, a multivariate analysis to determine relationships with birthweight, included analyses of primigravida only, as well as all gravida. Analyses were run utilizing information prior to delivery and separately at delivery (for example, placenta weight). Phase III examines events subsequent to birth as a function of information available at birth. These results are summarized in the form of Empirical Risk Tables which describe the empirical probability of the negative outcomes within the first year of life as a function of birthweight, gestational age, race, sex and placenta weight. The structure of the manuscript has been formed into four sections: 1. Description, 2. Concomitant Events, 3. Antecedents, 4. Subsequent Risk. Emphasis for the text material over the past year has been on finalizing figures and tables. Virtually all are completed. The writing of the monograph is in progress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02062 - 10 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Minimal Brain Dysfunction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	P. L. Nichols	Research Psychologist	DNB NINCDS
Other:	Ta-Chuan Chen	Sr. Math. Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

OBFS, OD, NINCDS

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.00	.00	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02106 - 09 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Developmental Factors Associated with Mental Retardation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	P. L. Nichols	Research Psychologist	DNB NINCDS
	E. C. Bien	Research Psychologist	DNB NINCDS

COOPERATING UNITS (if any)
Dr. Peter Shaughnessy, University of Colorado Medical Center
Dr. Wallace Kennedy, Florida State University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
The purpose of this study is to identify predictors of mental retardation in a population of 37,000 children followed from the prenatal period to age 7. Risk factors were examined separately for severely and mildly retarded children, and for subgroups without an identified cause or major neurological abnormality. The incidence of mild retardation (1% in whites and 5% in blacks) and to a lesser degree, of severe retardation (0.5%) was inversely related to socio-economic status. Among the severely retarded, 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded groups as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroup of severely retarded with unknown etiology, perinatal risk factors include non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. Special studies of drugs taken during pregnancy and of the incidence of mental retardation in relatives were conducted. This investigation is completed and a monograph is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02107-09 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. Feinberg	Research Psychologist (retired)	DNB, NINCDS

COOPERATING UNITS (if any) W.R. Baldwin, New England College of Optometry; R.E. Hoover, Baltimore, Md.; R.P. Kling, Georgetown Univ. Hosp.; M.A. Whitcomb, Nat. Acad. of Sc.; S.Z. Wood, Washington, D.C.; F.A. Young, Wash. State Univ.

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes the analysis between visual abnormalities in NCPP children and predictor variables; anecdotal treatment based on case histories of unusual visual abnormalities; special studies of high-incidence disorders; case studies of the blind children; and, preparation of a monograph encompassing these subjects. Basic data analysis is complete and a draft manuscript of the findings was prepared and is currently being revised.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02108 - 09 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Developmental Factors Associated with Learning Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB,NINCDS
Other:	E. C. Bien	Research Psychologist	DNB,NINCDS

COOPERATING UNITS (if any)
Dr. Peter Shaughnessy, University of Colorado Medical Center

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study identified early behavioral, physical and family characteristics of children with average IQ scores and below average school achievement, approximately 3% of the NCPP population. Low achievers were compared with their IQ-matched academically successful controls on prospectively ascertained indices of cognitive and physical development and family environment. Cognitive deficits and behavioral problems in the preschool period were associated with low achievement at age 7. Socioeconomic status (SES) and family structure were better predictors of low achievement than were indices of physical development or medical status. Low achievers were born into low SES, large families, and two-thirds of them were boys. As preschoolers, they had more language difficulties and lower IQ scores than controls. At age 7, deviant behavior, verbal and non-verbal cognitive deficits, and neurological soft signs were present. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in predictors of unexpected academic failure. A monograph has been reviewed for publication and the revised version is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02109-09 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Comprehensive Analysis of the NCPP Data on Congenital Malformations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: N.C. Myrianthopoulos Research Geneticist DNB NINCDS

COOPERATING UNITS (if any)
C.S. Chung, Univ. of Hawaii; H. Lubs and M.L. Lubs, Univ. of Miami, Fla.; J. Frias, Univ. of Florida; M. Melnick, Univ. of S. California, Los Angeles; P. Koslowe, Johns Hopkins Univ., Baltimore

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.00	2.00	1.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This long-term project is a primary area within the program plan for analysis of NCPP data. The objectives are to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical signficance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02112-09 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Neonatal Hyperbilirubinemia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Drage Chief DNB, NINCDS

COOPERATING UNITS (if any)
P. C. Scheidt, USUHS, Department of Pediatrics
J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.03	0.01	0.02

CHECK APPROPRIATE BOX(ES)

☒(a) HUMAN SUBJECTS ☒(b) HUMAN TISSUES ☐ (c) NEITHER

☒(a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The neonatal hyperbilirubinemia study has been designed to assess the relationship of intermediate levels of serum bilirubin on the subsequent neurological and mental development of NINCDS Collaborative Perinatal Project children. There has been increasing concern that neonatal serum bilirubin levels between 10-20 mg% may be damaging to the central nervous system, not in the classical sense of 'kernicterus' associated with levels above 20 mg%, but rather damaging in more subtle yet clinically significant ways. Neonates have been studied in five birthweight-gestational age categories, by three socioeconomic classes, for a variety of outcome measures, including mental and motor assessment at age 8 months, and a spectrum of neurological findings at age one year which will include motor performance, reflexes, tone, abnormal movements, eye findings and the overall neurological classification of normal, suspect or abnormal. The analysis of Phase I of this study has been published. The analysis of Phases II and III, which include data obtained at ages four and seven years, has been completed. A report on findings is being prepared.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02169 - 08 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Obstetrical Medication and Development in Infancy and Early Childhood

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: S.H. Broman Acting Chief, MRLDS DNB,NINCDS

COOPERATING UNITS (if any)
Dr. Peter Shaughnessy, University of Colorado Medical Center
Dr. Yvonne Brackbill, University of Florida

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.08	.06	.02

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study investigated relationships between obstetric medication and physical and cognitive development through age seven. Subjects were full term infants born to mothers with uncomplicated pregnancies and deliveries. The cohort was drawn from two hospitals in the NCPP. Pharmacological agents evaluated were inhalation anesthetics and six other drugs administered during labor and delivery. Outcomes in the first year of life included items from pediatric and psychomotor assessments. Later outcomes were scores from psychometric examinations, and items from a pediatric neurological examination. Univariate associations between outcomes and drugs were identified, and the significant relationships were examined in multiple logistic regression analyses with other risk factors included. The results suggest that inhalants are associated with deficits in early psychomotor and neuromotor functioning, and that oxytocin is also associated with psychomotor deficit. Scopolamine and secobarbital are related to respiratory difficulties in the newborn, and inhalants, scopolamine, and secobarbital are associated with palpable liver at 4 months. At older ages, scopolamine is associated with slightly lower scores on some cognitive tasks, and oxytocin is associated with lower achievement test scores. A report is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02171-08 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Compendium of Heritable Disorders of the Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: N.C. Myrianthopoulos Research Geneticist DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.10	0.05	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose is to prepare and maintain a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02234-07 DNB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Febrile Seizures Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS
PI:	D.G. Hirtz	Expert Consultant	DNB NINCDS

COOPERATING UNITS (if any)

OBFS, OD, NINCDS

LAB/BRANCH

Developmental Neurology Branch

SECTION

Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The NINCDS Collaborative Perinatal Project has provided a large prospectively defined pediatric population, unselected for level of risk, in which to investigate the prevalence and natural history of the most common convulsive disorder of childhood, febrile seizures. A series of papers has delineated the natural history of febrile seizures, identified risk factors for unfavorable outcome, and reviewed the effect of sample selection on outcome. An NIH Consensus Development Conference on Long-term Management of Children with Febrile Seizures was held. Results of the consensus conference have been published in professional and lay journals, and the papers were edited for a monograph, published in 1981. A major study to evaluate the effects of medications and of recurrent seizures is soon to begin under contract. We have collaborated in designing a study on the EEG as a predictor in febrile seizures, and in a survey on management of febrile seizures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02332-05 DNB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analysis of NCPP Twin Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: N.C. Myrianthopoulos Research Geneticist DNB NINCDS

COOPERATING UNITS (if any)

NHLBI; M. Melnick, University of Southern California, Los Angeles

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.50	0.40	0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a secondary area within the program plan for analysis of NCPP data. The objectives of the project are to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

TAB 6 -- STROKE & TRAUMA PROGRAM -- STP

ANNUAL REPORT
October 1, 1981 -- September 30, 1982

Stroke and Trauma Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 -- September 30, 1982

Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke

INTRODUCTION

The Stroke and Trauma Program (STP) of the NINCDS is responsible for research in the areas of stroke, cerebrovascular disease, brain, spinal cord and peripheral nerve trauma, nervous system regeneration, primary and metastatic brain tumor, pain, positron emission tomography and other related subjects. These areas and neurologic disease entities in terms of their high incidence, prevalence, morbidity and mortality, exact an enormous toll in human suffering. Included are the vast number of head, spinal cord and peripheral nerve injuries, the considerable number of strokes and their sequelae, the problems of preservation and regeneration of neuronal function following these diseases, brain tumor and chronic pain. High priority, therefore, is given to applied and clinical investigations with direct relevance to the pathogenesis, diagnosis and treatment of these diseases. With prevention of such diseases as the ultimate goal, understanding of the basic pathophysiologic processes is fundamental to such achievement. The program contains discrete, as well as overlapping components of basic, applied and clinical research and utilizes the several administrative instruments of program support (i.e., research project grants, program project grants, clinical research center grants, cooperative clinical trials, resource contracts, and service contracts).

The allocation of research funding within STP during FY 81 was:

Stroke and Cerebrovascular Disease	34%
Positron Emission Tomography	15%
Cerebral, Spinal Cord and PNS Trauma	23%
Regeneration and Plasticity	20%
CNS Neoplasm	4%
Other	3%

During that year, 227 applications were assigned to STP as being relevant to its mission. Of those, 71% were approved by initial review groups with concurrence from the NANCDS Council and 40% were funded. Of the total number of grants assigned to STP, 29% were funded as opposed to 40% in the preceding year. STP is served by several study sections and special review committees. The median priority score of all approved grants during the year was 229 versus 222 in the previous year. This numerical increase in median priority of some 7 points occurred while the median score for NINCDS as a whole decreased by 7 points. During the year, the approval rate of grants improved significantly presumably as an indication of better scientific merit, while the funding rate decreased to an effective level which was only 73% of the prior year.

The Cerebrovascular Research Centers are major interdisciplinary research and teaching efforts within STP and constitute a significant segment of the Stroke Program. The thirteen current centers serve as a focal point for research on etiology, natural history, diagnosis, treatment and pathophysiologic events related to cerebrovascular disease. These individual research programs are broad, multidisciplinary and only interrelated in a general sense. They all,

however, focus on specific studies of either a basic or applied nature, designed to provide a better understanding of the biochemical and pathophysiologic events secondary to ischemia and hypoxia.

The Comprehensive Stroke Center Program is completing its final phase with the write-up of the individual as well as composite data generated by each of the centers. Intercomparative information in some 2,000 patients will provide important research hypotheses for future studies.

Positron Emission Tomography (PET), an Institute-sponsored effort, is beginning to generate important research information as newly acquired equipment within the PET centers comes on-line. Early studies are verifying cerebral blood flow, metabolism and physiology, both in normal patients at different ages as well as in others with a variety of pathologic conditions. Newer compounds with either C^{11}r F^{18} tracers are being evaluated, particularly from the point of view of short half-life isotopes which allow multiple studies. During the course of the next two years, the Positron Emission Tomography Program will be developing and presenting massive amounts of useful information to the research community as a result of these early efforts.

Trauma to the head and spinal cord remains a major therapeutic entity. The bulk of cerebral trauma research is carried out in the Head Injury Clinical Research Centers with more highly targeted efforts in the Comprehensive Central Nervous System Trauma Centers. Currently, the management of severely injured patients in highly sophisticated intensive care units with extensive diagnostic and monitoring equipment has reached a plateau. Scientists are now turning to the cellular and molecular events occurring within traumatized tissue in order to understand the biological basis of injury. The same thrust is being taken in spinal cord injury research to provide additional information on the secondary and cascading events related to the immediate time period around the spinal cord injury. Clinical trials in the spinal cord injured patient are examining the value of high dose corticosteroid. A new clinical trial is being developed to evaluate the efficacy of high doses of barbiturates in the treatment of severe head-injured patients with uncontrolled increased intracranial pressure. While prevention of these injuries remains an ultimate goal, it nonetheless is imperative that the head and spinal cord-injured patient must receive prompt attention both to minimize and/or correct injury as well as to avoid long-term disability.

Emphasis is placed on research in central nervous system regeneration and plasticity as a complement to the head and spinal cord injury programs. Much of the information derived from either lower invertebrates or the head-injured patient may be applied directly to spinal cord injury or vice versa. While the basic properties of regeneration and plasticity must be unravelled in the laboratory setting, the clinical events surrounding spinal cord injury and its subsequent effects can be studied through the activities of the Comprehensive CNS Trauma Centers as well as the Spinal Cord Injury Clinical Research Centers. A careful evaluation of this patient population will allow development of appropriate stratification and prognostic factors which will aid in the design of future clinical trials.

Clinical investigators with advanced training in a scientific discipline remain in short supply. Yet, as research becomes more complicated, the equipment more sophisticated and the area of concern more molecular in nature, the need for training astute clinical investigators becomes more critical. Great emphasis

must be given to the recruitment and development of scientifically trained clinicians through the use of traineeships, fellowships and teacher-investigator development award mechanisms.

The NINCDS Stroke and Trauma Program, utilizing the funds and other resources made available to it, has served as the institutional focal point for the planning and operation of research endeavors in cerebrovascular disease, brain and spinal cord trauma, brain tumors, regeneration and other related research. This encompasses applied approaches, as well as efforts directed toward understanding basic disease processes, with the expectation of eventually preventing or ameliorating these diseases and their sequelae. The limited resources available, now and in the forseeable future, require a continuing re-evaluation of program goals and objectives to obtain the best possible research in all areas of endeavor so as to improve the quality of patient care with these diseases, and eventually prevent them.

I. CEREBROVASCULAR DISEASE

The 13 Cerebrovascular Research Centers are designed to foster interdisciplinary research, to maximize the sharing of stroke research resources, to attract young investigators to research in stroke related areas, and to provide a framework for collaborative discussion and interaction.

Studies at Cornell University Medical College during the past year illustrate the variety of approaches being used to investigate human and experimental stroke and related problems. Clinical studies include development of a large computerized data base with information on natural history, determining effect of early damage on outcome, and assessing effects of early treatment. Quantitative techniques are being developed to estimate brain water content by computerized tomography scan. A prospective study using Doppler ultrasound technique has been initiated to examine the carotid arteries of hypertensive and non-hypertensive industrial populations with asymptomatic bruits. Neuropsychological evaluation of auditory recognition and extinction in stroke patients continues as part of a long-term investigation of parietal lobe function. Quantitative histochemical and blood flow studies are being conducted in animals to characterize changes in brain following several types of controlled ischemia. Damage to the blood-brain barrier appears to be critical in determining whether or not edema follows cerebral ischemia. Permeability studies are in progress employing biochemical, radionuclide, and ultrastructural techniques. Hematologic studies in the laboratory have demonstrated a strong anti-platelet effect of indomethacin and prostacyclin (PGI_2) in a carotid thrombosis animal model. Studies in rat neonates of remote brain lesion effects on locus ceruleus is providing information potentially relevant to cerebrovascular injuries in infants and which, may yield possible mechanisms for recovery. Detailed maps of noradrenergic and adrenergic neurons in the brain which subserve cardiovascular control are being constructed in a search for a neurochemical basis for hypertension.

The Cerebrovascular Research Center at the Mayo Foundation has access to a unique data resource which provides a record of long-term trends indicating the frequency and distribution of the various categories of stroke, survival, and other aspects of the natural history of stroke. This record system assures nearly complete identification of all residents of Olmstead County, Minnesota who receive any form of medical care either as an in-patient, out-patient, in the emergency room or even when seen at home or in a nursing home. Because of the standard methods of continuing to update the record system, and because of the long history of neurologic

expertise in the community, long-term observation of trends in the occurrence of stroke in this community has been assured. Investigators at the Mayo Foundation are also interested in proton nuclear magnetic resonance (NMR) as a practical medical imaging modality. They are determining the sensitivity and specificity of NMR in detecting cerebrovascular disease and comparing the results with those obtained from CT. The findings from NMR are being correlated with cerebral biochemical alterations, particularly those involving water, lipids, and proteins in cerebral infarction. It is hypothesized that NMR imaging is more sensitive than CT in the detection of cerebral ischemia and infarction during the early stage, and that the alteration seen with NMR during the early stages of cerebral infarction results from a change in water content, whereas the alterations in later stages are from a change in the lipid or protein content.

During the past year, investigators in the Center at Washington University, St. Louis, Missouri, have begun regular studies of surgical candidates for superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis using techniques developed by them for the measurement of local cerebral blood flow, blood volume, and oxygen utilization employing positron emission tomography (PET). As a result of these studies, new insight has been gained into the hemodynamic consequences of stenotic lesions in the internal carotid as well as the middle cerebral artery. In such patients (often asymptomatic at the time of the study) they have now observed significant reductions in blood flow accompanied by the reductions in oxygen consumption and rather striking increases in local cerebral blood volume. They interpret such findings to mean that viable tissue exists in this area of threatened infarction, but that normally operative autoregulatory processes have been exhausted. This latter observation is strikingly underscored by the presence of the increased blood volume indicating substantial post-stenotic dilation of the cerebral vasculature. In conformation with their working hypothesis, they have seen such changes totally reversed by the STA-MCA anastomosis procedure. These data clearly indicate the potential efficacy of pre-surgical studies to identify individual patients who would be appropriate candidates for the anastomotic procedure.

An operational model has been developed in the St. Louis Center for in vivo analysis of dopamine receptors using PET. The strategy is based on the ability to simultaneously measure tracer behavior in brain areas rich in receptors (e.g., caudate nucleus) and an area with no receptors (i.e., cerebellum). Using data collected sequentially from these two regions, investigators can estimate the density and the permeability of the blood-brain barrier to spiperone. This model has been tested using ^{14}C-spiperone and direct tissue sampling in animals. Results of these studies have been extremely encouraging to date. They are now awaiting the synthesis of ^{18}F-spiperone to begin actual in vivo studies.

Studies at the Massachusetts General Hospital have demonstrated the potential usefulness of positron imaging in stroke disease and the volume of the $^{15}O_2$ equilibrium-imaging technique in providing quantifiable indices of blood flow and metabolism. On the basis of tomographic blood flow and oxygen metabolism images, patients with stroke have been classified as: (1) relatively free from evidence of damage; (2) with substantial evidence of ischemia but without necrosis; and (3) with necrosis. The impetus for these studies stems from the realization that acute stroke can be treated in a rational way only if one can reliably determine the physiological status of the injured tissue, both at rest and, after a therapeutic challenge.

At the University of Miami, research has traditionally been oriented toward better understanding the metabolic consequences of cerebral ischemia. More recently, the areas of interest have been extended to include the disciplines of neurophysiology, neuropsychology, neuropharmacology, and hematology. A report from this Center on "Mechanisms of Irreversible Injury in Cerebral Ischemia" was presented at the Princeton Conference.

Current interest has centered around two major areas concerned with pathogenetic mechanisms of ischemic brain injury: (1) the factors responsible for heterogeneity of ischemic injury within graded ischemic foci; and (2) the contribution of lipid peroxidative processes to the production of ischemic brain injury. A reproducible model for focal cerebral hemispherical ischemia containing consistent gradients of hemodynamic severity has been developed which makes it possible to assess separately the mechanisms of ischemic injury in the central versus marginal portions of an ischemic focus. Other studies in this laboratory suggest that lipid peroxidation by free radical reactions may be a factor restricting the post-ischemic recovery of energy metabolism in brain and that lipid-soluble antioxidants in brain may act to mitigate the extent of eventual brain damage.

A new program has been established at Rush Presbyterian St. Lukes Medical Center with the overall objective of enhancing knowledge concerning the role of prostaglandins in the pathogenesis, prevention, and treatment of stroke. This interdisciplinary effort includes investigators with expertise in coagulation, cell culture, radioimmunoassay, biochemistry, neuropathology, pharmacology, and medicinal chemistry. Preliminary studies have demonstrated the presence in human serum of an active component which binds prostacyclin (PGI_2) and prolongs its biological activity. This active compound has been found to be markedly reduced in patients with thrombotic stroke and attempts are being made to purify this factor so that its physical and chemical properties can be determined. The ultimate objective is to apply these investigations to the early diagnosis and prophylaxis for patients who are predisposed to stroke because of abnormalities in PGI_2 stability. Other projects include the use of long-term cultures of endothelial cells to study a prostacyclin-stimulating factor and the development of a model of thrombosis to clarify the roles of prostacyclin and thromboxane in experimental vascular thrombosis.

Clinical Trials

The Extracranial/Intracranial Arterial Anastomosis Study (EC/IC) was initiated five years ago with the objective of determining whether this surgical procedure would reduce by 50% or more, the incidence of first or recurrent completed strokes in patients with certain forms of cerebrovascular disease (as detailed in the clinical and radiological entry criteria for the study). As of July 31, 1982, patient accrual is expected to close, at which time there will be a total of approximately 1,450 patients from more than 60 centers in North America, Europe, and Japan. Years six, seven, and eight will provide for necessary patient follow-up. Year nine will be the year for final data accumulation, analysis, and publication.

The high patency rate of about 90% following the surgical procedure speaks to the quality of the participating surgeons as well as the feasibility of the procedure. The considerable difficulties inherent in a multi-center study have been successfully met to a great extent by this diligent and sophisticated group. The NINCDS Monitoring Committee selected for this study continues to meet regularly and is completely satisfied with the conduct of the study.

Another cooperative study was initiated at the University of Iowa with the objective of decreasing the morbidity and mortality from ruptured intracranial aneurysms by determining the optimal time for surgical obliteration of the aneurysm. Over 2,000 cases have been entered from seventy-five Centers and projected completion of case registration is March, 1983.

Research Grants

A new research project grant has been awarded to Boston University to expand the Framingham Stroke Study. There will be a detailed risk factor evaluation for stroke during the next two Framingham cycle examinations, approximately two years apart. This will extend the prospective findings of the Framingham Study on stroke up to 30 years of follow-up and will include the age group 75-84. A number of precursors will be evaluated about which little has been previously available. These include the role of arrhythmias documented by 1-hour ECG monitoring, echocardiographic findings of valvular and myocardial dysfunction, lipid profiles including HDL and LDL cholesterol, physical activity status, menopausal status, psychosocial factors including Type A behavior, carotid bruit, ecolyzer-confirmed smoking history and glucose tolerance based on a blood glucose load and other variables. Also to be done are two methods of measuring carotid artery stenosis. A more careful delineation of type of stroke will also be accomplished by using CT scan information as well as the clinical findings.

There is a paucity of information about vasogenic brain edema, the most commonly encountered form of brain edema in clinical practice which is generally seen in association with ischemic and hemorrhagic strokes, trauma, infections, or tumors, and involves primarily cerebral white matter. A project has been initiated at Washington University to evaluate the hypothesis that the polyamines and their rate-limiting synthetic enzyme ornithine decarboxylase play an important role in the pathogenesis of vasogenic brain edema and the break down of the blood-brain barrier.

A new investigator at Henry Ford Hospial is studying a frequently neglected aspect of stroke, the neuropyschological functioning of patients with transient cerebral ischemia, and progressive or complete cerebral infarction after carotid endarterectomy and extracranial/intracranial arterial bypass surgery. A neurobehavioral battery including psychological tests, neurological data, and behavioral sampling, are being employed to assess patients preoperatively and post-operatively over eighteen months. The results of neuropsychological assessment are correlated with data from serial angiography and Doppler sonography. Medical and neuropsychological results are being studied for their relationship to demographic or health history factors.

Metabolic regulation of cerebral blood flow is a widely accepted hypothesis, but the mechanisms whereby the brain regulates its own blood flow is obscure. A recent addition to the list of possible factors linking blood flow and metabolism is the purine nucleoside adenosine, which has been proposed as a metabolic regulator of coronary blood flow. In order to test this hypothesis, investigators at the University of Virginia are using a multi-faceted approach to study the cerebrovascular physiology and metabolism of adenosine in whole brain, in cerebrospinal fluid, and in pial vessels *in situ*. A comprehensive understanding of the control of cerebral blood flow will allow a more rational treatment of its alterations in disease status.

II. POSITRON EMISSION TOMOGRAPHY

Cerebral blood flow is a critical variable linked to metabolism and physiology in a wide variety of normal and pathological conditions. Iodoantipyrine labeled with the positron-emitting radionuclide ^{11}C has been synthesized by investigators at the University of Miami School of Medicine who have validated the suitability of this product for the measurement of regional cerebral blood flow in the rat as a prelude to its possible application as a blood flow tracer in human studies involving emission tomography.

For functional studies, a method has been developed for producing ^{11}C-2-deoxyglucose as a replacement for ^{18}F-2-deoxyglucose as a tracer. The shorter half-life of the ^{11}C compound lowers radiation exposure to subjects and makes it possible to perform sequential studies in a subject on the same day.

Normal brain homeostatic mechanisms regulate intracellular pH within narrow limits. Deviations from normal are associated with many neuropathological processes, both structural and metabolic in nature. Since cerebral pH affects important processes, e.g., blood flow, it is desirable to be able to assess the acid-base status of the brain using non-invasive methods applicable to human conditions. An evaluation has been made of the potential applicability of 5,5-dimethyl-oxazolidine-2,4-dione (DMO) for PET studies of cerebral acid-base balance. Results from animal studies indicate that this biochemically inert and non-toxic compound may be a useful agent for investigating cerebral acid-base balance using PET techniques.

At the University of California, Los Angeles, studies of aphasics using ^{18}F-Fluorodeoxyglucose positron emission computed tomography have shown areas of metabolic depression in the left hemisphere larger than the area of infarction noted on x-ray computed tomography. To evaluate the relationship between language abnormalities and metabolic depression, 11 patients had fluorodeoxyglucose metabolic scans, the Boston Diagnostic Aphasia Examination (BDAE), and the Porch Index of Communicative Ability (PICA). Local cerebral metabolic rates for glucose were determined for 13 brain areas as leftto-right ratios. Performance on several of the BDAE tests (auditory comprehension, naming, oral reading, and repetition) correlated significantly ($p < 0.01$) with altered metabolic ratios in the parietal and posterior middle inferior temporal areas; neither Broca's nor Wernicke's areas showed such correlations. The findings suggest that areas posterior, inferior, and superior to the traditional Wernicke's area (in and around area 22) are important in the language abnormalities in this group of aphasics.

While a number of neurological disorders are primarily or entirely manifested in white matter, myelinated brain regions are relatively inaccessible to current clinical imaging techniques. Although transmission computer tomography has proven invaluable in the clinical neurosciences, its use in the selective imaging of myelin is limited by the minimal difference in intrinsic electron densities of white and gray matter. Furthermore, in some disease of white matter there may be little or no alteration in tissue density, thus minimizing the diagnostic value of transmission tomography techniques. In order to overcome these problems, some property other than tissue density must serve as the basis for a myelin imaging technique. The development of positron emission tomographic techniques facilitates the design of a suitable method, since PET permits measurement of the regional distribution of administered radiotracers rather than of tissue electron density.

The PET Center at the University of Michigan has employed a test probe, iodobenzene, labeled with iodine^{123} to image myelin non-invasively in the monkey. Myelin imaging will be useful in evaluating various therapeutic regimens which may be proposed in the future to halt or to reverse the demyelinating process. Myelin imaging will also be useful for the detection of space-occupying lesions confined to white matter which are currently not visible by other techniques.

At Brookhaven National Laboratory research continues on the preparation of positron emitters, particularly carbon^{11}, nitrogen^{13}, and oxygen^{15} as well as the radionuclide fluorine^{18}. This research is focused on development of new methodology involving targetry and precursor production utilizing a small "medical cyclotron" which was recently installed. New synthetic methods for introducing fluorine^{18} into organic molecules are being explored along with new syntheses of labeled sugars for studying glucose metabolism, neuroleptics for in vivo receptor studies and compounds for probing specific enzyme activity. The "pro-drug" concept is used to improve delivery across the blood-brain barrier and studies on animals are performed to determine bio-distributions, radiation dosimetry, as well as the toxicity of the proposed radiopharmaceuticals in the brain and other organs. The Brookhaven group has led in the development of new positron-emitting radiotracers and has done much to disseminate this technology to other institutions.

III. SPINAL CORD INJURY

Spinal cord injury remains an extremely costly biomedical problem. As a result of accidents, war-related injuries, and a variety of disorders, an unacceptable number of young adults, young men in particular, are relegated to limited and dependent futures as paraplegics. It is estimated there are 10,000 new cases of spinal cord injury each year and a population of about 200,000 paraplegics in the United States.

Injury to the spinal cord may be followed by a succession of secondary effects that appear responsible for much of the ensuing disability and mortality. Most often, paralysis follows, at some distance in time, the causative injury, since severing of the spinal cord directly from a penetrating object is relatively rare. More often, the spinal cord is "bruised" by a transmitted mechanical force as might occur in an automobile collision. Neural tissue response to trauma includes swelling, diminished blood flow and/or bleeding within the spinal cord. It is anticipated that when the factors leading to these secondary effects are better understood, more effective treatment of spinal cord injury will result and disabilities such as paraplegia kept to a minimum or reversed. Thus, spinal cord injury research is being directed at several major questions. These include (1) explanations for the secondary (and presumably reversible) "self-destructive" reactions of the injured spinal cord to mechanical injury; (2) the development of sensitive diagnostic procedures to assess the extent of spinal cord dysfunction (as well as retained function); and (3) the adoption of appropriate therapeutic interventions to minimize the structural and functional sequelae of spinal cord trauma.

The five Spinal Cord Injury Research Centers, supported by the NINCDS, continue to be major contributors to fundamental and clinical research in the area of central nervous system trauma. The centers are located at Yale University, Medical University of South Carolina, New York University, University of Texas, San Antonio, and Ohio State University. While a common goal binds the centers, and while some research themes are common to several centers, each has developed

unique interests which serve to give the broadest coverage to the problems associated with spinal cord injury.

The research programs at Yale, South Carolina and New York University combine both clinical and basic science studies while the programs at Ohio State and Texas are devoted specifically to fundamental aspects of the spinal cord injury problem.

The research team at Yale is exploring the nature of physical forces impacting on the vertebral column and its enclosed spinal cord, the effect of the initial injury on subsequent blood flow within the cord, and control of urinary bladder function after injury (paraplegics often die of kidney infections related to poor bladder control).

Investigators at the Medical University of South Carolina are refining the use of electrical stimulation techniques and electrical recording from the central nervous system to improve upon existing diagnostic techniques. This should allow physicians the opportunity to better understand the extent of injury and permit initiation of more appropriate modified therapy. Since most spinal-cord injured patients are in a state of "spinal shock" for days after the injury, it is very important to develop laboratory measures for ascertaining the extent of the injury as early as possible in the shock period. This group is also determining the effects of various tissue constituents, e.g., calcium and potassium ions, on the injured nervous system since these substances may well contribute to the cord's degeneration after injury.

The research group at NYU continues to pursue basic studies of the tissue environment, including chemical interactions and the generation of potentially harmful by-products following injury. Blood clotting factors are under scrutiny as are factors that may destroy the membranes of the spinal nerves. Refined diagnostic procedures, e.g., evoked potential methods, developed in the laboratories are being introduced into the clinical research and care facilities. The group has also proposed several clinical studies of drugs reputed to minimize the consequences of spinal injury in experimental animals, such as naloxone, steroids and thyrotropin releasing hormone (TRH).

Researchers at The University of Texas are studying the degree of disability (and recovery) as a reflection of the components of the spinal cord that are injured (and spared) following trauma. They are also searching for the cause and pharmacological modification of exaggerated muscle reflexes that appear in affected muscles following injury.

The research center at Ohio State University focuses on a very fundamental approach to the biological manifestations of spinal cord injury. Efforts are underway to discern the effects of trauma on cellular energy systems and the enzymes that degrade the insulating membranes of nerve tissue.

Whereas, the aforementioned studies reflect different approaches to a common problem, a number of the centers are addressing similar questions. These include changes in metabolism, blood flow and clotting factors, and characterization of intact neural circuits following injury.

The NINCDS and other federal and private agencies support a number of spinal cord injury individual research projects throughout the country. These studies

provide insight into fundamental aspects of the disorder which when better defined should serve as a basis for novel therapeutic interventions. Reports from two of these laboratories in the past year have implied potential therapeutic effects for several commonly available pharmacological agents. Studies conducted at the Walter Reed Army Medical Center suggests that administration of naloxone immediately after injury may significantly improve recovery. However, a major problem associated with use of naloxone in the treatment of severe spinal cord injury relates to the fact that it also blocks the action of pain killers frequently needed by the injured patient. As a result, investigators are now seeking pharmacologically related substances that are capable of reversing the effects of injury which will not interfere with the alleviation of pain. A recent study from the Uniformed Health Services Medical School has suggested thyrotropin-releasing hormone (TRH), a naturally occurring substance, as a potentially useful alternative, and additional research is being carried out in this area. Although these findings have stirred considerable interest within the research community, additional efforts are required to substantiate these early findings, to ascertain possible adverse effects, to optimize the treatment regimen, and to more fully understand the mechanisms of the drug's actions. The NINCDS plans further studies to corroborate the initial findings.

The National Spinal Cord Injury Study (a Yale University-based, multi-institutional, clinical program encompassing several of the spinal cord research centers and other clinical facilities throughout the country) is in the final phase of evaluating two steroid dosages for possible therapeutic use in acute spinal cord injury.

IV. HEAD INJURY

The principal effort of clinical research groups, until recently, has been to demonstrate the capability of specialized treatment centers to effect reductions in mortality following severe head injury. More contemporary attempts to delineate prognostic indicators of survival and quality of life are now well advanced. While there may be small variations from clinic to clinic, it is now possible to show that a generally agreed upon hierarchy of indicators is being established.

Non-invasive multimodal evoked potentials and the electroencephalogram are found to be exceptionally effective in predicting outcome during the acute phase following brain injury. Furthermore, they allow subsequent frequent monitoring of critical changes in brain function to rapid adjustment of therapeutic activities in relation to such changes. One research group has reported that multimodal evoked potentials are accurate predictors of outcome in 80% of all cases and closer to 90% when non-neural complications are excluded. The certainty is reputed to grow still further if the following factors are taken into consideration in descending hierarchical fashion, i.e., surgical mass lesions, age, intracranial pressure, pupillary response, extraocular motility and motor posturing.

Another clinical correlation with important implications for the patient, the community and clinical practice is the finding that recovery from surgical intracranial decompression is a function of the time from injury to surgery. Delay from injury to operation of less than four hours results in a mortality rate of 30%, whereas surgery performed after four hours is characterized by as much as a 90% mortality rate. In this instance, other relevant prognosticators include the results of the initial neurologic examination, sex, multimodal evoked potentials and post-operative intracranial pressure.

The future management of head-injured patients may change significantly as a result of recent additional findings. One such case in point is the perceived need for monitoring intracranial pressure. There is now evidence to suggest that acutely head-injured patients with normal CT (computerized tomograms) need not have intracranial pressure monitoring routinely, since the pressure is probably not elevated. However, repeat CTs at 24-48 hours are important in sustaining this assurance, particularly if the clinical status of the patient deteriorates.

Although brain injury has received considerable research attention, considerable differences of opinion still remain regarding the pathophysiological sequelae. At least one investigative group has indicated that the concept of diffuse post-traumatic brain edema in the acute phase may have been overemphasized. This group proposes that greater emphasis be placed on changes in cerebrovascular tone or cerebrovascular volume, and on intracranial pressure. Adoption of these perceptions would necessitate associated changes in therapeutic regimens, i.e., controlling vascular tone and responsiveness, rather than edema in the acute phase.

Prostaglandins have been implicated in the damage sustained by cerebral arterioles via arterial hypertension after brain injury. Their mechanism of action is dependent upon generation of free oxygen radicals. Research into the factors contributing to neural injury following ischemia indicate that the advent of recirculation may further jeopardize neural tissues, since the generation of prostaglandins in blood vessel walls requires recirculation. Thus, further insight into the vascular mechanisms associated with blood stasis may result in the implementation of more effective therapeutic measures subsequent to trauma.

Earlier clinical studies and therapeutic trials were often initiated with patients exhibiting varying degrees and locations of injury. However, a number of research opportunities have illustrated the need for better discrimination in the selection of patient cohorts for specific therapeutic studies. For instance, at least two types of comatose patients have been described on the basis of differences in cerebral blood flow and oxygen utilization. Another categorizing approach yields two subgroups of severely brain-injured, discernible on the basis of early death (within 48 hours) or not. These two cohorts are divided between those with severe homogenizing necrosis and/or direct brain stem damage (and concomitant oculovestibular alterations) versus those with hematoma and attendant symptoms. The former derive in large measure from high speed auto accidents and appear to represent the current irreducible mortality associated with severe head injury. The latter derive from falls and blows and include many individuals who are ultimately salvageable. Therefore, only by careful analysis of neurological, pathophysiological and neuropathological factors can series of patients be compared effectively and treatments evaluated meaningfully.

Several years ago, questions arose as to whether indiscriminate release of neurotransmitters, including epinephrine, occurred following injury to the brain, and whether the transmitter release was responsible for deleterious secondary effects (e.g., ischemia, edema and hypoxia of the brain) subsequently observed. While the latter concept has yet to be substantiated, an increase in norepinephrine has been shown and that increase is found to be inversely related to the Glasgow Coma Scale. Alert patients, after brief loss of consciousness, have normal levels, while those in coma have as much as seven times the normal level. Blood pressure, pulse and temperature are elevated proportionally to elevations in plasma norepinephrine in patients with head injury. The questions raised now are

the possible broad range, adverse effects of sympathetic hyperactivity in patients having sustained severe head injury. These repercussions could include hypermetabolism, cardiovascular abnormalities, as well as direct effects of catecholamines on the damaged brain. This line of inquiry is in keeping with a new found emphasis on the contributions of other organ systems and local homeostatic mechanisms (e.g., acid-base balance) to recovery from severe brain injury.

A variety of investigative methods and diagnostic techniques continue to be developed and refined. New laboratory methods of imparting injury to the brain have evolved, including approaches that cause graded damage due to acceleration and torque. Thus, injuries commonly sustained by humans now can be rather faithfully reproduced in experimental animals, including primates. These models enable better definition of the injury, and will permit the testing of potential therapeutic interventions in much more meaningful contexts than hitherto possible.

The CT scan continues to be explored for its full potential. For instance, one recent study suggests that the variations in the CT number in edematous brain are directly related to the protein content of the edema fluid. Such findings greatly extend the interpretative capability of these already valuable instruments.

A number of pharmacologic agents are reputed to protect the injured brain from secondary adverse effects. Several clinical trials to evaluate the protective effects of barbiturates are currently underway or nearing completion. The acquisition of appropriate data is necessarily slow and deliberate and detailed results will not be available for some time. Dimethyl-sulfoxide (DMSO) is also suggested as an aid in reducing post-injury brain damage. Several research groups have manifested interest in and proposed the conduct of trials using this agent. However, problems related to toxicity of the substance and/or protocol of the study remain to be overcome before definitive results will be forthcoming.

A broad spectrum of clinical and fundamental investigations are performed at the five head injury research centers supported by the NINCDS. The centers are located at the Virginia Commonwealth University, University of Pennsylvania, University of Texas at Galveston, Albany Medical College and New York University. The results of a number of the studies performed at these centers have been cited earlier. Program projects at the University of California at San Francisco and the University of Texas at Houston are engaged in somewhat more focused fundamental and clinical research. The former program concentrates on brain edema, while the latter is concerned with respiratory control, blood coagulation and psychological indicators as they relate to the pathopysiology of brain injury and recovery therefrom. The NINCDS also supports eight individual research programs devoted to such topics as quantitative characteristics of computerized tomography, compensation in rehabilitation, pathology of minor head injury, behavioral alterations as a result of specific lesions and changes in neurotransmitter and receptor function following injury.

V. CNS NEOPLASMS

Research related to brain tumor, biology and metabolism, as well as related diagnostic and therapeutic research, remains a primary thrust within STP. Progress has been made in determining the fine structure of a series of virus-induced experimental brain tumors (RG2, 9L, H-54, AVM sarcoma, etc.). Utilizing horseradish peroxidase as an experimental marker, studies have delineated permeability characteristics, the interrelationship of subcutaneous brain tumors with

intracerebral tumors and the variabilities observed in the growth and biology of these systems. Quantitative autoradiographic studies will be used to more specifically define fine structure relationships. The CT scan has also been utilized for demonstrating presence of tumor in animal models as well as for more specifically defining the areas in and adjacent tumor. During the forth coming year, greater emphasis will be placed in determining the capillary and endothelial defects which occur in experimental gliomas.

Utilizing two types of monoclonal antibody unequivocal identification of neuroblastoma cells has been demonstrated in bone marrow of patients harboring this disease. Increased efforts toward staging patients and learning more of the tumor biology are underway. The interrelation of the mouse neuroblastoma C1300 with that in the human is being defined.

Radiation sensitizers have the potential of increasing the efficacy of radiation therapy. Research in experimental models has attempted to establish a dose-response curve versus comparative neurotoxicity for a series of these sensitizers and, in addition, develop quantitative functional tests. The concentration X time and exposure characteristics for the development of neurotoxicity in relation to electron affinity and lipophilicity are being determined. Thus far, the metabolic product of misonidazole (desmisonidazole) is approximately two times less toxic than misonidazole itself. The location of peripheral nervous system lesions and the types of axonal degeneration are being defined. Further goal of research in this area is to develop protectors that might avoid the development of neurotoxicity.

Basic research into nerve growth factors (NGF) as they may pertain to tumor growth and differentiation provides important insight into regulatory mechanisms. During the course of the year, investigators examined the sensitivity of NGF receptor sites, mechanisms of controlling the affinity of NGF binding and promoter substances to several different compounds. Specific cell lines sensitive, resistant and unresponsive to NGF are being examined to determine their morphological and biochemical differences.

Specific effects of adenosine include induction of neurite extension. However, adenosine also prevents proliferation when it is delivered in lesser concentrations. Adenosine has been shown to mimic three of the effects of NGF. The demonstration that the major site for adenosine activities occur extracellularly, has led investigators to use genetic approaches to better understand its mechanism of action.

Utilizing the neuroblastoma cell line, the interaction of NGF, growth rates, maturation, culture and tumor-age relationships have been examined. Sensitive, resistant and unresponsive neuroblastoma lines have been identified and thus provide the nidus for further research. Utilizing the same cell line, other researchers examine the functions of methyltransferase and its subcellular distribution. Further research into the regulation of growth and differentiation will be undertaken utilizing a tumor model which is highly reproducible, demonstrates constant growth rates, metastasizes, secretes markers (catecholamines) and is eventually lethal.

Scientists are producing monoclonal antibodies with high specific activity that are designed to recognize and differentiate tumor from normal brain. Such

antibodies can then be utilized for the study of the early development of tumors and biochemical analysis of antigens involved in these antibody reactions. Patients with neuroblastoma, for whom monoclonal antibodies have been developed, are now able to be studied in greater detail. Utilizing the athymic nude mouse, investigators are analyzing the predictive potential of direct subcutaneous transplants of human brain tumors.

VI. NEURAL REGENERATION AND PLASTICITY

Current results of experimental work related to regeneration and plasticity represent the broadest and fullest expression, to-date, of research in this area. Using a wide variety of approaches, a critical mass of investigators has uncovered fundamental concepts that promise to absorb the efforts of numerous researchers seeking to unravel the enigma of regeneration in the central nervous system.

A fuller realization of the heterogeneity of neural and non-neural tissues within the normal central, peripheral and autonomic nervous systems has led to major reassessments of the complexities involved in reconstituting essential neural components in damaged tissues.

Although there has been a suggestion that some recovery of function through regeneration may be observed in mammals, e.g., following lesions of long tracts in neonatal rats, recent findings reveal that the observed returns of postural and locomotor function are a reflection of either redirection of evolving tracts over uninjured substrates, or reflexes intrinsic to the spinal cord below the level of the lesion. In non-mammals, e.g., goldfish and sea lamprey, the most common repair following spinal injury appears to involve regeneration, collateral sprouting and synapse formation over relatively short distances. An exception to the latter is reassertion of the long spinal tracts of amphibians after cord transection during metamorphosis. Obviously, a wide range of experimental models is helping establish the principles of neural development and repair. The worth of these models for regeneration research is evident.

The nature of the research questions posed and the methodologies employed are changing drastically. Earlier years were characterized by the search for appropriate experimental models and the use of relatively uncomplicated morphological and electrophysiological methods to describe experimentally-induced alterations of the nervous system. However, current studies, while dependent upon the same survey techniques, have become increasingly more discriminating, permitting evaluation as far as the molecular and ionic levels. Discrete localization of specific cells, their membrane receptors, neurotransmitters, and biosynthetic processes has been achieved through such techniques as cell injection, freeze-fracture, immunocytochemical labeling, histochemical reactions, microchemical assays and molecular probes. The physiological properties of cells and their environment are explored by ion-selective electrodes, fluorescent markers and optical detectors. These and other powerful analytic methods are permitting exploration at a heretofore unimagined level of detail.

Several laboratories are looking at "growth associated proteins" in the regenerating optic nerve-tectal system of the goldfish. They are also using radiolabeled glucose and amino acids to study the nature and speed of the retrograde message and biosynthetic turn-on observed in neurons following axonal injury.

Interest continues to grow regarding the macromolecular changes occurring in cell membranes during neurite extension, e.g., following the application of Nerve Growth Factor to responsive neurons and related cells. The progression of events is leading toward investigation of cellular reprogramming at the level of gene function.

An intricate picture of neurotrophic functions and interactions is currently emerging. Trophic factors appear to run from the relatively non-specific to the very specific, and their sources seem to vary considerably. Thus, a battery of bioassays appear necessary to discern the functional capability of potentially active trophic substances. For example, Ciliary Neuronotrophic Factor (from chick eye) has no significant trophic activity for lumbar cord neurons, while trophic factors for the latter are present in conditioned media of Schwann or muscle cells. The complexity of trophic function may be exemplified by the observation that ciliary ganglion neurons cultured on polyornithine substrate in media containing Ciliary Neuronotrophic Factor (and serum) will grow neurites only if the polyornithine substrate is presented with Polyornithine-binding Neurite Promoting Factors; these released into the medium by several types of cells or exuded by explanted ciliary ganglia themselves.

There is growing recognition that the central nervous system undergoes intrinsic changes beyond those of the acute phase of injury. Dendrite and synaptic reorganization may result in significant changes in sensory, motor and reflex or effector function. The significance of these alterations to the organism and their relative reversibility remain to be more fully explored.

Attempts to restore function following injury to the nervous system must, of necessity, take into account a broad array of biological factors virtually unimagined a few brief years ago. An initial momentum has been achieved in our attempts to understand the repair of neural systems. This impetus must be sustained and strengthened in the effort to overcome the ravages of injury and disease of the central nervous system.

VII. PAIN

Pain is one of the most prevalent and costly national health problems. When it persists beyond the usual course of a disease, or normal healing time for an injury, or is associated with progressive disease, pain may be termed chronic. Investigators at the University of Washington have conducted research on the effectiveness of relaxation and biofeedback, and more recently, directed attention toward determining the efficacy of operant conditioning, hypnosis and cognitive behavioral therapy approaches in alleviation of chronic pain. Both, biofeedback and muscle relaxation training have been shown to reduce tension and migraine headache activity. Biofeedback appears to be no more efficacious, is far costlier than relaxation training and has been of limited value in the treatment of chronic pain. Lengthy in-patient operant treatment programs appear to increase physical activity levels and decrease medication use, at least while the patient is in a controlled hospital environment. Cognitive-behavioral treatment approaches have also been shown to alleviate pain in a variety of pain syndromes. In order to explore the potential for therapy involving combined approaches, these investigators have devised a comprehensive multidimensional assessment of patient, process, and outcome variables which should enhance conclusions that can be drawn from the results.

At the University of Kansas Medical Center, a clinical trial is being conducted to study the overall comparative efficiency of propranolol and amitriptyline in prophylaxis of migraine and the clinical and psychological variables associated with the therapeutic effect for each drug. During the past year, the effectiveness of propranolol in migraine prophylaxis has been correlated with measurements of physiological effects and plasma levels. In twenty-six migraine patients there was a highly significant relationship beteen the prophylactic effect of the drug and its beta-adrenergic blocking effect, with no such relationship to plasma drug levels. Two statistical studies of the headache-prone population utilizing a headache questionnaire instrument have been completed. Both studies utilized factor analysis to investigate the natural grouping of variables occurring in headache patients.

Interest in the spinal cord gray matter surrounding the central canal (lamina X) stems from the recent demonstration that the region receives a projection from primary afferent nociceptors and contains several pain transmitters known to be related to pain transmission. Electrophysiological studies at the University of Minnesota have revealed that a significant neuron population in this area is responsive to nociceptive stimuli delivered to highly restricted receptive fields. Furthermore, these neurons within lamina X are capable of coding information regarding the location of a noxious stimulus on the body surface and transmitting such information to several brainstem nuclei.

Investigators at the University of Texas are investigating the possibility that Zoneperiac, a prostaglandin synthesis inhibitor might affect nociceptive responses of spinothalamic cells. Preliminary studies indicate that there may be a central action of the substance in addition to any peripheral local action.

Ongoing studies at the University of Massachusetts are directed toward defining the mechanical sensitivity of afferent neurons innervating joint capsules. A recently developed technique allows the measurement of afferent responses while simultaneously measuring regional strain of the joint capsular material.

Two additional investigations have been initiated this year. One, at the University of Iowa, will pursue studies designed to confirm or deny the hypothesis that acute stress-induced elevations in arterial blood pressure, resulting from exposure to either conditioned or unconditioned adversive stimuli, may become sustained because changes in the baroceptor reflex arcs reduce the aversiveness of environmental stimulation. The second, at Harvard University, is aimed at understanding mechanisms of activation of pain sensory endings and sensitization of the endings, by use of tissue culture techniques which will allow direct visualization of pain neurons and response to pain-specific stimuli.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1981 -- September 30, 1982

Institutions

1. University of Rochester (N01-NS-8-2385)

2. American Heart Association, N.C. Affiliate, Inc. (N01-NS-8-2386)

3. University of Oregon Health Sciences Center (N01-NS-8-2387)

Title: Comprehensive Stroke Center

Contractor's Project Directors: 1. John H. Feibel, M.D.
2. James E. Toole, M.D.
3. Frank M. Yatsu, M.D.

Current Level of Support: 1. $ 73,300
2. $150,000
3. $ 50,000

Objectives: The objectives of these Centers are to:

a. Conduct a program of applied clinical research in which fundamental advances are utilized in the development of specific approach for the prevention, diagnosis and management of cerebrovascular disorders.

b. Develop integrated and coordinated community resources to evaluate the results of research on the prevention, diagnosis, and treatment of cerebrovascular disorders.

c. Demonstrate to physicians, other professionals and the public, by a broad public education program, the significant advances in cerebrovascular research and management.

Major Findings:

The Comprehensive Stroke Center Program, currently in its fourth year as a cooperative undertaking is directed toward developing and evaluating treatment models for stroke patients in three geographically distinct areas, the northwest (Oregon), northeast (Monroe County, NY) and the mid-southeast (North Carolina).

Investigators in these centers have generated base-line patient data information in an attempt to demonstrate that the transfer of currently employed therapeutic modalities into the community does have an effect on outcome, morbidity, and mortality of the stroke patient and that uniform data and observation techniques are feasible.

A large amount of comparable data including demographic, diagnostic, and outcome factors is being authenticated. Cross-center comparison tables of this data have been prepared and a preliminary analysis of survivorship across the three centers is in progress.

Significance to NINCDS Program and Biomedical Research: As research in the Stroke Clinical Research Centers has progressed, questions have arisen regarding the applicability of their efforts. Do any of the techniques developed at a particular clinical research center reach the surrounding community hospitals? If so, does their application there produce the same results as it does at the Center? Does the presence of a Center affect the distribution of care of the stroke community? Does the care given in the Center affect mortality or morbidity for a given type of stroke? Will intensive rehabilitation efforts help in some cases? The Comprehensive Stroke Centers are attempting to find answers to these questions.

Proposed Course: The three Centers have developed certain research areas which are somewhat independent, while retaining programs with a certain degree of overlap. During the fourth year, the collection and analyses of patient data have been done in accordance with guidelines established jointly by the three Centers.

Contractor	Termination Date
University of Rochester	6/28/83
North Carolina Health Association, Inc. (now Am. Heart Assoc., N.C. Affiliate, Inc.	5/31/83
University of Oregon Health Sciences Center	6/14/83

The completion of this work and the publication of its results is expected during FY 82-83.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1981 -- September 30, 1982

Institutions

1. University of California, San Diego (NO1-NS-9-2312)

2. Albert Einstein College of Medicine (NO1-NS-9-2313)

3. University of Texas Medical Branch (NO1-NS-9-2314)

Title: Establishment of a Comprehensive Central Nervous System Trauma Center

Contractor's Project Directors:
1. Lawrence Marshall, M.D.
2. Kamran Tabbador, M.D.
3. Ralph F. Frankowski, Ph.D.

Current Annual Level of Support:
1. $220,000
2. $220,000
3. $240,000

Objectives: This program is intended to evaluate the availability and the efficacy of the care of patients with CNS trauma, and to develop guidelines for optimal care of these patients in the setting of their community resources. Beyond these broad goals, specific objectives will be to:

1. Develop coordinated community resources by means of which developments in CNS trauma research can be evaluated on a community basis.

2. Foster clinical research on improved diagnosis and treatment of patients with CNS trauma.

3. Bring results of research on CNS trauma rapidly and effectively to the general community and especially to those segments of the community with a high incidence of CNS trauma.

It is anticipated that such centers will serve as a general guide to the development of improved facilities for patients with CNS injury in other communities with similar geographical and population characteristics.

Major Findings: The three geographically distinctive centers have completed gathering much of their comparative epidemiological data on CNS trauma and are collaborating on a number of manuscripts intended for publication in appropriate national and international journals. Further evaluation is underway regarding development of optimal interactions between the emergency medical services and the trauma treatment centers. A number of publications intended to alert and inform the public, with respect to nervous system injury, have already appeared. The three centers are actively engaged in the implementation of a number of research projects, interest and need for which derive from their earlier studies.

Significance to NINCDS Program and Biomedical Research: A survey of CNS trauma in the United States revealed approximately 400,000 new cases of head injury, severe enough to be hospitalized. Approximately one half of these cases were 24 years old or younger. Due to the youth of those incapacitated, the impact on national health and productivity is evident. Because of this, the NINCDS has had special interest in the problem of CNS trauma, and is supporting research, both in basic studies aimed at clarifying the pathophysiology of brain and spinal cord injury and in clinical studies designed to improve diagnosis and treatment, particularly in the period immediately following the injury. Through its programs of head injury and spinal cord injury research, information important to patient care is being obtained. New diagnostic techniques and new forms of treatment are being evaluated in specialized clinical research units. In view of the increasing amount of research in this field, it is now appropriate to evaluate this new information at the community level and to contribute to its utilization.

Proposed Course: It is expected that two additional years of support (at a reduced level) will be needed to complete existing and already planned research, demonstration and education projects. Irreversible functional deficits, including coma, are not infrequent consequences of head injury, cardiac arrest, and other medical problems leading to a compromised blood supply to the brain or its components. Barbiturates are reputed to suppress the sequelae of cerebral ischemia and hypoxia when given soon after insult. Suggestions have been made that when given in appropriate amounts and at the proper time the drugs appear to (1) afford protection from focal infarction, (2) permit resuscitation from global ischemia-anoxia, and (3) control intracranial hypertension. The direct barbiturate effects involved in the protective mechanism may include reduction of metabolism, cell membrane stabilization, free radical quenching, and anesthesia. A prospective, randomized clinical trial on the efficacy of barbiturates in moderating the effects of severe head injury, specifically increased intracranial pressure, is being initiated. Physiological and clinical paramaters will be evaluated during barbiturate treatment for otherwise uncontrollable increased intracranial pressure. Since great uncertainty remains concerning the effect of barbiturate treatment on the injured and ischemic brain, this cooperative clinical study holds promise for establishing the value of a pharmacologic intervention that is being practiced in a number of locales without well-established proof of efficacy.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1981 -- September 30, 1982

Institutions

National Institute of Mental Health (YO1-NS-9-0044-04)

Title: Safety and Efficacy of Cingulotomy for Pain and Psychiatric Disorders

Contractor Project Director: Herbert Pardes, M.D.

Current Annual Level of Support: $83,128

Objectives: The research will assess therapeutic outcome, neurologic status, and behavioral test performance in consecutive patients who have undergone bilateral stereotaxic anterior cingulotomy for the relief of persistent pain or for the alleviation of severe psychiatric disease. The purpose is to interview and examine such patients both before and after operation to permit evaluation of the postoperative findings in relation to the preoperative baseline for each patient. In this way it should be possible to specify which diagnostic groups are helped by cingulotomy and which are not, and one can document the duration of any palliative effects. The proposed work will also permit the investigators to describe the neurological and behavioral effects of the surgical procedure, whether transient or lasting, in quantitative terms.

Major Findings: After cingulotomy, patients with chronic pain rated the intensity of their clinical pain significantly lower than they had before operation, and matched their clinical pain to significantly lower temperatures delivered by the Hardy-Wolff-Goodell dolorimeter. They also had superior discrimination performance after operation as compared with before, indicating that the improvement in their clinical pain was not attributable to a decrement in pain perception. In contrast, no such changes in clinical pain were seen after subcaudate tractotomy. In fact, the subcaudate tractotomy group had significantly elevated temperature matches after operation. Nevertheless, their postoperative discrimination scores showed significant improvement, suggesting a dissociation of mechanisms underlying clinical and experimental pain. Patients who received noninvasive treatments for chronic pain matched their pain after treatment to lower temperatures than they had before. At the same time, they were more willing to call hot or mildly painful experimental stimuli painful than were patients in the other two treatment groups. It is surprising that this tendency to give many reports of pain did not preclude a successful outcome. The investigators are inclined to predict that the benefits for this group will be transient.

Significance to NINCDS Program and Biomedical Research: Pain is the most common symptom of disease which compels patients to seek medical counsel. In its acute form pain has an important biological function. It prepares the individual to cope with injury or disease, and is a diagnostic tool for the physician. The acute form is usually self-limiting due to the acute nature of the pathologic process. Chronic pain, however, may have no biological function yet cause extreme hardship for the affected individual, the family, community and workplace. The costs to the American public have been estimated to be as much as $50 billion

annually. This study analyzes the efficacy of a surgical method of last resort that is employed to alleviate otherwise intractable chronic pain.

Proposed Course: To continue to follow the protocol of the on-going longitudinal study.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1981 -- September 30, 1982

Institutions

1. Hahnemann Medical College and Hospital, Philadelphia (NO1-NS-2-2307)

2. Georgetown University School of Medicine, Washington (NO1-NS-2-2310)

Title: Standardized Reproducible Spinal Cord Injury Model

Contractor's Project Directors: 1. Perry Black. M.D.
2. Jean R. Wrathall, Ph.D.

Current Annual Level of Support: 1. $568,000
2. $470,700

Objectives: This program, initiated September 29, 1982, is intended to (1) develop an animal model of reproducible spinal cord injury and (2) use the model to test drugs and other means purported to minimize the consequences of injury to the spinal cord.

Major Findings: This program has just been funded.

Significance to NINCDS Program and Biomedical Research: There are approximately 200,000 spinal injured in the United States, with approximately 10,000 more individuals sustaining these injuries each year. The physical, emotional, and financial drain is enormous, especially so in light of the youth of those incapacitated. "Novel" therapies, to minimize the disability (paraplegia and quadriplegia), are proposed periodically. The NINCDS is seeking an appropriate animal model to permit well controlled trials of reputed treatments for spinal cord injury.

Purpose Course: The two phases of study require (1) validation of a reproducible model(s) of spinal cord injury and (2) use of the model(s) to test those therapies considered most promising at the time the model is established.

TAB 7 -- OFFICE OF THE DIRECTOR OF INTRAMURAL RESEARCH -- ODIR/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Office of the Director, Intramural Research Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report of the Scientific Director
of the
National Institute of Neurological and
Communicative Disorders and Stroke

October 1, 1981 through September 30, 1982

The Intramural Research Program (IRP) conducts research in the neurosciences through the direct operation of its laboratories and clinics on the main NIH campus as well as at off-site locations in Rockville and Frederick, Maryland; at Woods Hole, Massachusetts; and on the Island of Guam. In these facilities, Federal Government scientists and support personnel continue to make major contributions to the field's explosive growth. Ranging from basic neurobiologic probes to clinical trials of new therapeutic agents, this work continues to advance our ability to prevent, ameliorate or cure neurologic and communicative disorders. The impressive accomplishments of Program scientists are summarized in subsequent sections of this report. This section will primarily address managerial issues impacting on current and future IRP operations.

Maintenance of the Program's creative vigor and breadth of scientific inquiry, despite fluctuating and generally shrinking resources, remains as the principle challange to IRP management. Not only must existing, high quality, programatically relevant investigations obtain adequate support, but some new initiatives must also be launched if the Program is to exploit critical methodological and conceptual advances and remain at the forefront of neurosciences research. An approach to these objectives includes rigorous quality assessments of current activities, careful restructuring of priorities, timely reallocation decisions, and vigorous efforts directed towards the retention and/or recruitment of scientific talent. Unfortunately, fiscal and personnel constraints, some unique to agencies of the Federal Government, not infrequently complicate the rational operation of these processes.

Notwithstanding claims from some in the Extramural community, the IRP is not growing at the expense of the Institute's grants program. As in the past, IRP's financial situation reflects that of the NIH generally and of the NINCDS specifically. Since 1979 approximately 11-12% of the total NIH appropriation went for the support of all intramural operations; for NINCDS this proportion has remained essentially level at 13-14%. At the same time, grant support increased from 61 to 66% for all of NIH and from 66 to 72% of total appropriations for NINCDS. A decline in the Institute's research and development contracts, from 10% in 1979 to about 5% in the current fiscal year, provided the bulk of funds for the expansion of the grants program.

In terms of actual total dollars allocated, IRP received approximately $38 million in fiscal year 1982, an increment of $3 million above the preceding year. When computed in constant dollars, however, the Program's total allocation has remained essentially unchanged during the past two years and is now about 4% less than in 1979. Moreover, a steadily rising proportion of this total is now channeled towards such uncontrollables as personnel costs (up from 30 to 36% of total expenditures since 1979 due to manditory salary increases) and overhead changes (up from 30 to 33% during the same period). As a result, while the amount of residual "other objects" dollars available for the purchase

of laboratory equipment and supplies has remained virtually constant since 1979, actual purchasing power has fallen by more than 25%. This decline has forced a reduction in the overall size of IRP operations, as well as deferrals of planned equipment replacements and laboratory renovations. Relief from this trend towards increasing budgetary stringencies is not expected in the immediate future.

IRP research contracts, by funding such critical activities as reagent synthesis and off-site primate holding, provide essential support for high priority in-house investigations. As mentioned previously, the Institute's total expenditure on research and development contracts declined sharply during the past two years. The reduction in the IRP contract portfolio, while less drastic, still amounted to over 10% during the past three years. This cutback, compounded by the effects of inflation, compelled a shift in direction for some research projects and a curtailment in the size of overall Program operations. Unless the IRP is to undergo major alterations in the nature and scope of its investigative efforts, research contracts must be protected against further erosions in their funding levels.

During the past year, IRP operated without any formal ceiling on the total number of employees or periods in which the hiring of new staff was prohibited. In response to these rather unique circumstances, Program size largely reflected budgetary and spatial constraints. The net effect was that the number of IRP scientific and support personnel remained essentially constant. At the end of May 1982 the Program had 500 employees: 210 were in full-time-permanent and 186 in other-than-full-time-permanent positions; another 104 occupied ceiling free positions (54 Visiting Fellows, 36 Guest Workers, and 6 Intergovernmental Personnel Act employees). Considering this total group, 49% are classified as scientists, 37% as technical support personnel, and 14% hold administrative positions. In the scientific group, 32% have Government tenure (22% occupy Civil Service positions and 10% are in the Public Health Service), while 68% are nontenured (32% Visiting Program, 21% Fellows, and 15% in various other categories such as Inter-governmental Personnel Act and special expert programs).

The number of individuals occupying IRP training positions also continued at essentially stable levels. During the past year 179 promising young investigators took advantage of opportunities to train here as Staff Fellows (63); Visiting Fellows, Associates or Scientists (74); Guest Workers (36); and Intergovernmental Personnel Act investigators (6). In addition, a newly instituted program of elective courses for medical and dental students attracted 13 students during the past year. Since most who apply for one of the four 8-week sessions offered each year seek maximum exposure to neurosciences research, a major component of their experience is an involvement with an on-going clinical or laboratory project. This is usually handled on a tutorial basis arranged by the chief of the laboratory or branch that has selected the student. Another training activity deserving special mention is the EEO Summer Employment Program for high school, undergraduate, and graduate students. This program provides on-the-job training with a view towards encouraging talented students to pursue research careers in the neurosciences. During the past summer IRP employed over 80 young people in this program, with the proportion of minorities exceeding that of any other NIH Institute.

The relative constancy in overall Program size disguises a continuing problem in the retention and recruitment of senior scientists. During the past year Dr. Donald B. Calne, who for the past seven years served ably as both Clinical Director and Chief of the Experimental Therapeutics Branch, resigned to accept a substantially higher paying academic post in Canada. Efforts to replace him have as yet been unsuccessful. Strenuous attempts to recruit a chief for the newly created Communicative Disorders Branch from a list of highly qualified candidates recommended last year by an external search committee have also been unrewarding. Similarly, long standing efforts to recruit leadership for the Program's positron emission tomography and epilepsy research activities have yet to be successfully concluded. These difficulties in no small measure reflect the inadequacies of current salary and fringe benefit packages offered by NIH to its highest level employees. For example, all four candidates interviewed for the Communicative Disorders Branch position reported earnings from their current academic positions 30 to 60% higher than the maximum NIH can pay.

The amount of on-campus space available for IRP use increased by nearly 7% during the past year as a result of the opening of the laboratory half of the fifth (NINCDS) floor of the Ambulatory Care Research Facility (ACRF). Much of this facility, which conveniently adjoins the NIH Clinical Center, has been assigned to the Experimental Therapeutics Branch, allowing consolidation of operations previously scattered about Buildings 10 (Clinical Center) and 36. Remaining ACRF laboratory areas have been dedicated to meet urgent Program needs for cold rooms, animal rooms, and a conference room. The clinical half of the ACRF, yet to be made available for Institute use, will house a greatly expanded range of outpatient research activities as well as provide facilities for the communicative disorders, epilepsy, and clinical neurophysiological activities. Program operations will soon be further benefited by the implementation of long standing plans to consolidate most IRP branches conducting patient research on the fifth floor of the Clinical Center. Leading off a complicated series of moves, the Neuroimmunology Branch will soon transfer from Building 36. Space vacated in Building 36 as a result of all these changes will permit the expansion of several preclinical laboratories, particularly the newly organized Laboratory of Molecular Genetics.

As a result of current operating stringencies, no major new research initiatives were undertaken during the past fiscal year. On the other hand, the shut down or size reduction of some IRP components enabled important shifts in Program emphasis. For example, the Neuroimmunology Branch received additional means to start a new section which will focus on disorders of the neuromuscular system; the Laboratory of Molecular Genetics received resources to augment recombinant genetic studies; the Laboratory of Molecular Biology began a new Section on Molecular Neurobiology; and support for Institute cerebral imaging studies involving positron emission tomography and nuclear magnetic resonance expanded.

Investigator initiated research by Program scientists continued to flourish during the past year. During this period 13 projects were initiated, 16 were completed or terminated, and 130 remained active. The most extensively supported disciplines in the basic neurosciences were physiology, chemistry, microbiology, and pharmacology. Investigations of demyelinating, dementing, and neoplastic disorders of the nervous system received the most support in the clinical research area. During the past year 37 new clinical research protocols were approved, 28 were terminated, and 87 remained active. Many of these studies involved tests of novel therapeutic agents, most of which are now categorized as drugs of little commercial value.

More than 300 scientific articles were published by IRP staff members during calendar year 1981. Journals publishing most IRP authored papers during this period included in the pre-clinical areas Brain Research, Journal of Neurochemistry, Proceedings of the National Academy of Science, Experimental Neurology, Science, Journal of Biological Chemistry, Nature, and in the clinical areas Neurology, Archives in Neurology and Advances in Neurology. An IRP-sponsored study of papers published between 1970 and 1976 by NINCDS intramural investigators compared with NINCDS extramural grantees found that in the basic neurosciences the number of times other authors cited articles written by members of the former group averaged 15.6 in contrast with 13.4 for the latter group. In the clinical neurosciences, intramural papers averaged 6.5 cites per article as compared with 5.6 for the extramural papers.

Each year a number of IRP scientists receive special recognition for the sustained excellence of their scientific contributions. These accolades include invitations to lead a major professional organization, present a prestigious lecture, serve on the editorial board of an influential journal, or to receive an important prize. Among those so honored during the past year Roscoe Brady, Chief of the Developmental and Metabolic Neurology Branch, deserves special mention. He received the Passano Foundation Award for "highly original contributions to our understanding of the inborn errors of lipid storage diseases known as Sphingolipidoses".

TAB 7.A -- NEUROEPIDEMIOLOGY SECTION, ODIR -- NES/ODIR

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Neuroepidemiology Section, ODIR
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
for Period October 1, 1981 through September 30, 1982
Neuroepidemiology Section
Office of the Director
Intramural Research Program
National Institute of Neurological and Communicative Disorders and Stroke

Bruce S. Schoenberg, M.D., Dr.P.H., Chief

The Neuroepidemiology Section is responsible for the development and implementation of epidemiologic and genetic programs to investigate the cause, prevention, and treatment of neurologic disorders in human populations. Emphasis has been placed on major neurologic diseases in which the diagnoses can be clinically verified to the satisfaction of skilled neurologists.

The Section is unique in being the only unit devoted exclusively to research in the epidemiology of diseases of the nervous system. These research studies require collaboration of many individuals. However, since there is a severe shortage of available manpower in neuroepidemiology, the Section developed an active teaching program for current and future collaborative investigators. A series of four videotapes produced by the Section are distributed on a loan basis without charge. A textbook, entitled NEUROLOGICAL EPIDEMIOLOGY: PRINCIPLES AND CLINICAL APPLICATIONS, was prepared, and a scientific quarterly journal entitled NEUROEPIDEMIOLOGY began publication in 1982. A symposium on the solutions to methodologic problems in neuroepidemiology was held in conjunction with the Society for Epidemiologic Research and the World Federation of Neurology. In co-operation with the World Health Organization and the World Federation of Neurology Research Committee on Neuroepidemiology, formal courses were conducted in Beijing, the People's Republic of China, Madrid, Spain, Florence, Italy, and Lima, Peru. Additional courses will be held in Mexico City, Mexico, Quito, Ecuador, and Caracus, Venezuela. A workshop on controlled clinical trials in neurology was held in conjunction with the American Academy of Neurology. Future symposia are planned in collaboration with the World Health Organization, the World Federation of Neurology, and the International Epidemiological Association. These sessions serve as a stimulus for neuroepidemiologic research on a worldwide basis. We are also providing opportunities for fellows to spend from six months to one year working with members of the Section in order to learn the techniques of neuroepidemiology. During the past two years we have had physicians from Great Britain, Nigeria, Mexico, Turkey, India, Spain, Italy, and Peru, and have received inquiries from Kenya, the People's Republic of China, and Israel for future opportunities. There is considerable neuroepidemiologic interest among senior neurologists (two of the physicians working in the Section are professors and chairmen of their own units abroad). Finally, current individual and institutional research training grant programs have been expanded to include neuroepidemiology. With the initiation of an educational program, the Section has focused on research investigations.

Epidemiologic studies have two basic requirements: uniformity and accuracy of data collection. This necessitates the use of a standardized, internationally accepted classification and coding system. The most recent scheme generated by the World Health Organization is seriously deficient with regard to neurologic disorders. The Section is therefore collaborating with the World Health Organization Neurosciences Program, the World Federation of Neurology, and the American Academy of Neurology to revise this system of classification and improve its usefulness for neuroepidemiologic research.

Another important problem for the neuroepidemiologist is the enormous cost of maintaining neurologic surveillance on a large number of patients. Therefore, we have attempted to utilize existing registries of neurologic disease, such as in a study of presenile dementia based on the Israeli National Neurologic Disease Registry. In addition, we have assisted British investigators in organizing information routinely collected through the British National Health Service on all neurologic inpatients in a section of London with a population of 3-1/2 million inhabitants. The utility and accuracy of these data have been demonstrated in a study of the Guillain-Barré syndrome. A similar registry has been organized for the population of northeastern Italy.

There have been a number of neuroepidemiologic case-control studies which have suggested associations between a given factor and a particular disease, but the number of patients has been inadequate for meaningful conclusions. We are working in collaboration with a number of multiple sclerosis clinics to establish a uniform protocol and data base to enable us to explore several hypotheses of interest which require a large number of cases. Similar arrangements are being made to initiate analytic epidemiologic studies of Alzheimer's disease. These several projects in support of research activities, have been initiated in conjunction with a very active research program.

With regard to neurologic problems in children, the Section documented the frequency of primary intracranial neoplasms in the pediatric population of Rochester, Minnesota, and the State of Connecticut. In addition, we investigated cerebrovascular disease in infants and children. The magnitude of this problem was documented for the first time. The study demonstrated that neonatal intracranial hemorrhage is relatively common (1.1 cases/1,000 live births), that it is strongly associated with prematurity and hyaline membrane disease, and that it is difficult to recognize clinically. For pediatric cerebrovascular disease unassociated with birth, trauma, or infection, the incidence rate was 2.5/100,000/year. These cases were further characterized by survival, residual disability, and cause (whenever possible). The clinical and angiographic features of children with moyamoya disease were examined in detail. This condition appears to be more common than suggested by early case reports. The Section is also investigating the epidemiology of cerebral palsy (CP). A study of temporal trends in the incidence rate of CP for Rochester, Minnesota, addressed the concern that advances in perinatal care, by rescuing the compromised neonate, are increasing the rate of neurologic handicap. It was gratifying to learn that in the population studied, coincident with a period of change in perinatal care, the incidence rate of CP declined. In a CP outcome study, a decreased survival was limited to

individuals who needed custodial or total nursing care. For the remainder of the case sample, a 100% 10-year survival prevailed, and resolution of the motor handicap was shown not to be an exceptional event. Case-control studies of the identified CP cases and of concurrent neonatal deaths are being initiated in search of maternal, fetal and obstetric risk factors of CP.

The Section has conducted extensive investigations of primary intracranial neoplasms. First, problems with nomenclature and disease definition were resolved. After this, two patterns of age-specific incidence emerged. Analyses of most population-based data worldwide revealed a small childhood peak, followed by a later peak between ages 50 and 80. Data for Rochester, Minnesota, however, showed the childhood peak, followed by an increasing incidence rate with increasing age. Careful study of this discrepancy showed 1) that the greater percentage of cases first diagnosed at autopsy in Rochester accounted in large part for this difference, and 2) that a substantial number of brain tumors remain undiagnosed in the elderly during life. Studies have just been completed to evaluate the role of computerized tomography in the diagnosis of brain tumors and to explain the recent increase in the incidence of pituitary tumors among women of childbearing age. The introduction of computerized tomography has not resulted in any increase in the reported frequency of these tumors in the Rochester, Minnesota population, while the apparent rise in the incidence of pituitary tumors seems to be the result of more sophisticated neuroendocrine diagnostic procedures. An exhaustive, critical review of a survey strategy to measure the national incidence and prevalence of intracranial neoplasms has been completed. In addition, racial differentials in the frequency of certain intracranial tumors (meningiomas and pituitary adenomas) are being examined. Investigations of the relationship between intracranial neoplasms and extracranial tumors have been especially rewarding. An association was found between the occurrence of breast cancer and meningioma in women. This result raises interesting etiologic possibilities when considered with other evidence: 1) meningioma is the only common intracranial neoplasm with a higher incidence in females; 2) the abrupt clinical appearance or enlargement of this tumor during pregnancy has been described; and 3) the finding of estrogen receptor protein in meningioma has been reported.

At the present time, there is little to suggest that improved medical management of the completed stroke will substantially affect the cerebrovascular disease problem. It would appear that greater benefit could be achieved by dealing with the precursors of stroke rather than delaying treatment until after the event has occurred. Therefore, a non-concurrent, prospective study of a cohort of 2,000 elderly individuals was undertaken to determine the role of heart disease and hypertension as risk factors for both transient ischemic attacks and completed stroke. When the case-control approach was applied to these data, different patterns of risk factors were demonstrated for transient ischemic attacks and completed ischemic stroke. While hypertension, diabetes mellitus, definite hypertensive heart disease, and valvular heart disease are important risk factors for completed ischemic stroke, these disorders have a substantial effect on the subsequent risk of TIA. When these data were analyzed in the format of a prospective study, it was possible to calculate the absolute risk of stroke as a function of the presence or absence of specific forms

of cardiovascular disease. The following types of cardiovascular disease yielded the highest ischemic stroke incidence rates (given in cases/1,000/year): myocardial infarction (15.5); congestive heart failure (20.5); and TIA (42.0). In considering risk factors for TIA, both angina/coronary insufficiency and congestive heart failure yielded the highest rates (10.4 and 10.9, respectively). Once etiologic precursors of stroke have been identified, medical intervention before the occurrence of long-lasting disability requires that there be an interval of time between the onset of the risk factor and the development of completed stroke. Analysis of data from this non-concurrent prospective study revealed that those developing borderline hypertension, valvular heart disease, or ischemic heart disease remained stroke-free for the initial one and one-half years after the first occurrence of each specific form of cardiovascular disease. This finding implies that there is an interval of time following the onset of these conditions when it may be possible to intervene medically to reduce the risk of stroke.

Other investigations in the area of stroke involve a careful analysis of unusual patterns of cerebrovascular disease (e.g., more than 20 TIA's/day).

Alzheimer's disease/senile dementia, despite its high apparent clinical frequency among the elderly, has not been well studied in a U.S. population. Because of this, we have launched three investigations. One is derived from a review of detailed clinical records utilizing a population-based, records-linkage system; the second utilizes a two-stage survey consisting of a questionnaire and clinical examination; and the third (in collaboration with the National Institute on Aging) is based on a questionnaire survey. In the records-linkage study, a neurologist using fixed diagnostic criteria reviewed records from all medical facilities serving the residents of Rochester, Minnesota. This made it possible for the first time to determine the incidence of dementia coming to medical attention in a well-defined U.S. population. For those age 30 plus, the incidence rate was 110 new cases/100,000 population/year. The rates increase with age, and the age-specific rates were higher in women. To confirm the reduced survival of demented patients reported on the basis of individuals hospitalized at specific medical centers, we examined the survival of all demented individuals identified through our records-linkage study. Dealing with an entire population minimizes any possible selection bias that may be present for a series of patients seen at a particular medical institution. The survival rates generated for all demented patients in the defined population were significantly reduced compared to age- and sex- matched survival statistics derived from life-tables for residents of the northwest central region of the U.S., thereby documenting in a community study previous observations based on hospitalized patients.

The two-stage survey permitted us to estimate the prevalence of dementia in a biracial community. For each race, prevalence ratios were higher for females. For each race and sex, the prevalence figures rise dramatically with age. This morbidity study indicates that dementia represents a major health problem for both racial groups.

There has been some debate as to whether Alzheimer's disease is a single disease entity regardless of its age at presentation. Since the

frequency of Alzheimer's disease is relatively low before age 60, an enormous population is required for surveillance in order to obtain an adequate number of patients for study. We are therefore utilizing the resources available through the Israeli National Neurologic Disease Registry to identify all potential cases among the population of Israel. These cases will be intensively reviewed to determine the accuracy of diagnosis and to explore a number of epidemiologic studies of the distribution and risk factors for this disease. A similar sex-ratio for patients with onset before and after age 60, and a steadily increasing age-specific incidence in the elderly would argue in favor of a single disease entity.

The Section is also interested in accurately documenting possible racial differentials in the prevalence of major neurologic disorders. A number of early investigations suggested possible differences by race, but were based on hospital or clinic experience and could not identify a well-defined population from which cases were derived. Population-based studies followed, but questions concerning the results centered on possible racial differentials in access to expertise in neurologic diagnosis and treatment. We reinvestigated (in conjunction with the Surveys and Demographic Studies Section, OBFS, OD, NINCDS) this problem of possible racial differentials in the prevalence of major neurologic disorders by surveying a well-defined population (approximately 25,000, almost equally divided between blacks and whites). We developed a strategy which eliminated the requirement that persons must have entered the health-care system for detection of disease. The disorders investigated included cerebral palsy, dementia, psychomotor delay, epilepsy, Parkinson's disease, essential tremor, and cerebrovascular disease (both transient ischemic attacks and completed stroke). The basis of the investigation was a door-to-door survey which utilized a detailed questionnaire inquiring not only about diagnoses, but also about signs and symptoms suggestive of neurologic dysfunction. Over 99% of the households agreed to the interview. Those household members suspected of having one of the disorders of interest were then asked to have a neurologic examination conducted by a senior, board-certified neurologist. The interviews and examinations have been completed, and the data are being edited and analyzed. Data currently available for Parkinson's disease indicate that in the population studied, parkinsonism is more common in whites but the difference between races is not as great as suggested by earlier studies. The same survey yielded information on essential tremor, thereby providing the first data on the prevalence of this condition in a defined U.S. population. For either race, the prevalence ratios were slightly greater in women, and for either sex, the figures were slightly higher for whites. In this same population, it was also possible to measure the prevalence of cerebral palsy. Prevalence ratios of cerebral palsy were higher in males than in females, and greater in blacks than in whites.

Similar strategies are being developed for application in developing countries (e.g., Nigeria, Mexico, the People's Republic of China, Peru, Ecuador, and India), in collaboration with the World Health Organization. Preliminary results from pilot studies in Nigeria and the People's Republic of China have already revealed interesting findings. For example, migraine

is as common among a rural black African population as among urban populations of Western Europe. Furthermore, epilepsy is a major problem in Nigeria, with a prevalence considerably higher than reported in developed countries. In an area of Beijing in the People's Republic of China, the prevalence of cerebrovascular disease is higher than anywhere else in the world where this problem has been studied.

We currently have very little information on the patterns of medical care received by all individuals with neurologic disease in a given community. The Section is, therefore, studying this problem in Rochester, Minnesota. Although the findings of this investigation will not necessarily be applicable to other regions of the U.S., the City of Rochester does offer particular advantages. Cases of neurologic disease among residents have already been identified through previous studies. Medical encounters are easily documented through a records-linkage resource. In addition, Rochester residents have access to high-quality medical care, and physicians with neurologic expertise are available within the community. Thus, the Rochester experience may provide some estimate of the pattern of medical care in the ideal situation in which the population has ready access to neurologic expertise, and in which there is little financial restraint to such care. The study for patients with brain tumor is being prepared for publication, and similar data are being analyzed for completed stroke.

Although death certificate data are limited by possible misdiagnosis, incomplete case ascertainment, errors in coding, etc., detailed morbidity information on neurologic diseases for the entire U.S. and for other countries is not available. The Section has analyzed mortality data for selected neurologic disorders by country and by county in the U.S. The overall patterns which emerge may be useful in evaluating trends over time and in formulating etiologic hypotheses. Among the most interesting findings is that the mortality from cerebrovascular disease has decreased in most developed countries over a 20-year period. This trend is not universal, however. For multiple sclerosis, countries initially reporting high mortality rates have generally reported declines, so that more recent mortality data for multiple sclerosis by country show less of a differential than previously reported. United States mortality rates for motor neuron disease and anencephaly were analyzed by county. For anencephaly, counties in the Mississippi River region and in the Appalachian Region had the highest rates. With regards to motor neuron disease, counties in the west (especially the northwest) had the highest rates and there was a positive association with rural farming. These leads will be pursued in more definitive studies.

A number of other collaborative projects include the investigation of space/time clusters of neurologic disease (with the Center for Disease Control and the Government of Colombia), the development of survey strategies (with the World Health Organization and the Section on Disease Statistics Surveys), a study of myasthenia gravis and multiple sclerosis in the same patient (with the Mayo Clinic), an investigation of neurologic disorders during pregnancy and the postpartum period (with the Mayo Clinic), a study of the epidemiology of eye tumors (with the Connecticut State Department of Health), the effect of weather on the incidence of stroke (with the Mayo Clinic), and international comparisons in the incidence of brain tumors. Finally, extensive reviews have been prepared

on the epidemiologic aspects of Huntington's disease, otitis media, Alzheimer's disease, cerebrovascular disease, primary intracranial tumors, Tourette's syndrome, peripheral neuropathy, neurologic diseases in the elderly, controlled therapeutic trials of motor neuron disease, epilepsy, descriptive, analytic, and experimental methods in neuroepidemiology, and statistical methods for calculating confidence intervals, and procedures for neuroepidemiologic investigations in developing countries.

The clinical neurogenetics component of the program involves three areas: 1) genetic-epidemiologic studies of movement disorders (e.g., the dystonias); 2) genetic-epidemiologic studies of multifactorial neurologic disorders (e.g., Parkinson's disease and multiple sclerosis); and 3) genetic and biochemical studies of hereditary nervous system tumors.

Collaborative studies are in progress to explain our earlier observations of altered dopamine beta hydroxylase and norepinephrine levels in blood and biopterin in CSF in a genetic subset of dystonia patients. Members of selected families are being brought to the Clinical Center, NIH, for trial of several new pharmacological agents.

In the area of multifactorial disease, we have now ascertained over 175 twin pairs and one set of quadruplets with parkinsonism. Clinical and genetic study of 41 monozygotic twin pairs and 79 dizygotic twin pairs, selected on the basis of at least one member being diagnosed as having Parkinson's disease, revealed only one monozygotic twin pair and none of the DZ group concordant for the disease. Although the unaffected co-twin in each case remains at risk, this very low concordance suggests that neither typical environmental nor genetic factors are critical determinants. Data on smoking support an earlier impression that there is a decreased risk for Parkinson's disease in smokers. Analysis of clinical and psychological observation and interview data on 21 MZ twin pairs discordant for Parkinson's disease is underway. If life-long differences in personality are present in affected versus unaffected twins, as our preliminary study suggested, a very early determinant for Parkinson's disease is indicated.

Three surviving quadruplets, one of whom has Parkinson's disease, have been extensively evaluated neurologically and psychologically. They, too, show the same life-long differences in personality as do the discordant monozygotic twins.

Over 140 MS twin pairs have been ascertained. Genetic-epidemiologic analysis of 51 pairs personally examined reveals higher, but not absolute, concordance in MZ twins. This suggests a significant genetic contribution as well as an environmental component. The fact that of 11 twin pairs concordant for MS, all are female, suggests that genetic factors may be sex-influenced. Early events found to be more frequent in affected MS twins include birth anoxia, frequent childbirth, serious infection, and surgery.

An apparently undefined leukodystrophy simulating MS with onset at about age 35 is under study in a kindred with over 20 affected. Tentative genetic linkage assignment has been made.

Studies in the area of hereditary tumors of the nervous system have focused recently on neurofibromatosis with bilateral acoustic neuroma. Efforts have been directed at improving and simplifying screening of high-risk individuals confirming diagnosis and establishing criteria for intervention. Audiologic studies, including evaluation of auditory-evoked response and acoustic reflex decay, appear to be a useful means for early documentation of acoustic neuroma and for following their effects.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01924-12 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Clinical, Genetic, Pathophysiologic Study of Hereditary Movement Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Roswell Eldridge	Medical Geneticist	NES	ODIR	NINCDS
Other:				
Thelma Koerber	Statistical Assistant	NES	ODIR	NINCDS
Peter LeWitt	Clinical Associate		ET IRP	NINCDS
Walter Lovenberg	Chief	Biochemical Pharmacology Section	HE	NHLBI
G. Constantopoulos	Research Biochemist	Clinical Investigations & Therapeutics Section	DMN IRP	NINCDS

COOPERATING UNITS (if any)

ET, DMN, IRP, NINCDS; HE, NHLBI; and Department of Neurology, University of Helsinki

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Clinical Neurogenetics Studies, Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.75	0.25	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In this project, we seek to 1) clarify and expand the nosology of the hereditary movement disorders; 2) contribute to the understanding of the underlying biochemical basis; 3) determine the most effective treatment for each disorder; and 4) suggest guidelines for counseling individuals at risk. General syndromes under study include the dystonias, tic disorders, Huntington's chorea, and myoclonus. Approaches include standard epidemiologic and clinical genetic studies together with collaborative efforts in evaluating the role of neurotransmitters such as dopamine, their precursors, and metabolites, and their necessary cofactors.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01927-12 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Clinical, Genetic, Pathophysiologic Study of Hereditary Nervous System Tumors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Roswell Eldridge	Medical Geneticist	NES	ODIR		NINCDS
Other:	Thelma Koerber	Statistical Assistant	NES	ODIR		NINCDS
	Anita Pikus	Audiologist		OPD		CC
	Barry Smith	Deputy Chief		SN	IRP	NINCDS

COOPERATING UNITS (if any)
OPD, CC; SN, IRP, NINCDS
Department of Surgery, Beth Israel Hospital
Department of Neurosurgery, Massachusetts General Hospital

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Clinical Neurogenetics Studies, Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.75	0.25	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In this project we seek to define and classify hereditary tumors of the nervous system; to add to the clinical description and natural history of these diseases; to suggest methods for early diagnosis; evaluate present modes of treatment; and develop methods for preclinical detection and screening.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02167-08 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Genetic Epidemiology Studies in MS and Other Multifactorial Neurologic Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Roswell Eldridge	Medical Geneticist	NES	ODIR		NINCDS
Other:	Thelma Koerber	Statistical Assistant	NES	ODIR		NINCDS
	Henry McFarland	Assistant Chief		NI	IRP	NINCDS
	James Dambrosia	Mathematical Statistician	OBFS	OD		NINCDS
	Christopher Ward	Visiting Scientist		LCS		NIMH

COOPERATING UNITS (if any)
NI, IRP and OBFS, OD, NINCDS; LCS, NIMH; Department of Neurology, University of Oregon; Department of Neurology, Rutgers University; and Department of Medical Genetics, University of Indiana

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Clinical Neurogenetics Studies, Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	0.5	2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In this project we are coupling genetic study with epidemiologic, immunologic, serologic and neurochemical studies in selected families and twin pairs with disorders due to multiple factors such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease.

To date, 14 presumptive "Multiple Sclerosis" families and 51 twin pairs with this condition have been the subject of three publications. Sixty-five twin pairs with Parkinson's disease have been the subject of two reports. Seven twin pairs with Alzheimer's disease have been ascertained.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02240-06 ODIR

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Epidemiology of Dementia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any) Epidemiology, Demography, and Biometry, NIA; W. Massey, M.D., Duke University; E. Kokman, M.D. and J.P. Whisnant, M.D., Mayo Clinic; B. Jordan, Harvard Medical School; M. Alter, Temple Univ.; E. Kahana, Hadassah Hospital, Jerusalem, Israel

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A number of different approaches are being utilized to estimate the mortality and morbidity of Alzheimer's disease/senile dementia in several population groups in the U.S. and to measure the distribution of this disease in segments of the population.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02241-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Epidemiology of Cerebrovascular Disease in Adults

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any)

J.P. Whisnant, M.D., Mayo Clinic; D.G. Schoenberg, M.S., Bethesda, Maryland; A. Lilienfeld, M.D., Johns Hopkins University

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.3	2.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This investigation is aimed (1) at evaluating the effect of heart disease and hypertension as potentially treatable precursors of completed stroke and transient ischemic attacks; (2) at documenting unusual patterns of cerebrovascular disease; (3) at determining the autopsy patterns for patients dying with cerebrovascular disease in a defined community; and (4) at examining if weather parameters have any effect on stroke incidence.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02243-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pediatric Neuroepidemiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
	Tatiana Kudrjavcev	Neurologist	NES	ODIR	NINCDS

COOPERATING UNITS (if any) D. Schoenberg, M.S., Research Epidemiologist, Bethesda, Maryland; J.F. Mellinger, M.D., M.R. Gomez, M.D., and R.V. Groover, M.D., Department of Neurology, Mayo Clinic; B.W. Christine, M.D., M.P.H., Connecticut State Department of Health

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Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	3.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project documented the frequency of primary intracranial neoplasms in the pediatric populations of Rochester, Minnesota, and the State of Connecticut. In addition, using the records-linkage system available for residents of Rochester, Minnesota, we investigated the magnitude and risk factors for cerebrovascular disease in infants and children. Temporal trends in the incidence rate of cerebral palsy as well as distribution of clinical subtypes and survival by clinical subtype were determined for the population of Rochester, Minnesota, for the years 1950-1976.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02297-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Mortality from Neurologic Disorders: National and International Comparisons

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
Other:	Nadir E. Bharucha	Visiting Scientist	NES	ODIR	NINCDS
	Roberta H. Raven	Guest Worker	NES	ODIR	NINCDS

COOPERATING UNITS (if any)
W. Massey, M.D., Duke University; D.G. Schoenberg, M.S., Bethesda, Maryland

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.7	3.7	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Although death certificate data are limited by possible misdiagnosis, incomplete case ascertainment, errors in coding, etc., detailed morbidity information on neurologic diseases for the entire U.S. and for other countries is not available. The Section has analyzed mortality data for selected neurologic disorders by country and by county in the U.S. The overall patterns which emerge may be useful in evaluating trends over time and in formulating etiologic hypotheses.

19 - ODIR/IRP (NES)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02299-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Reviews of Epidemiologic Aspects of Neurologic Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
	Tatiana Kudrjavcev	Neurologist	NES	ODIR	NINCDS

COOPERATING UNITS (if any)

W. Massey, M.D., Duke University; D. Schoenberg, M.S., Bethesda, Maryland

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.4	2.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Development of new neurologic studies requires thorough historic and methodologic reviews of prior investigations. These yield important unexplored etiologic clues that may be investigated using current technology. Major emphasis has been given to cerebrovascular disease, otitis media, inherited ataxias, Huntington's disease, febrile seizures, Tourette's syndrome, peripheral neuropathy, neurologic disease in the elderly, controlled therapeutic trials of motor neuron disease, epilepsy, descriptive, analytic, and experimental methods in neuroepidemiology, statistical methods for calculating confidence intervals, and procedures for neuroepidemiologic investigations in developing countries.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02300-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Clinical Course and Medical Care for Neurologic Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any)

J.P. Whisnant, Dept. of Neurology, Mayo Clinic, Rochester, Minnesota

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The study uses a review and abstraction of data from records for a selected group of neurological disorders. It obtains the items of data necessary to determine onset of the disorder, duration, date and cause of death, or current status. These data will be used to construct modified life tables to estimate the expectation of life after diagnosis, the survival curve and morbidity and severity estimates. It will also include analysis of type and duration of medical care received by patients with neurologic disorders derived from a well-defined population.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02301-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Collaborative Studies of Less Common or Less Debilitating Neurologic Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
Other:	Tatiana Kudrjavcev	Neurologist	NES	ODIR	NINCDS

COOPERATING UNITS (if any)
M. Zack, M.D., Atlanta, Georgia; Neurosciences Program, WHO, Geneva, Switzerland; D. Duane, M.D., B. Sandok, M.D., Mayo Clinic

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A number of collaborative efforts involve the investigation of the characteristics of unusual or less debilitating (e.g., headache) neurologic disease phenomena. Unusual associations or space/time clusters of neurologic disorders may provide leads to etiology or therapy. These may be tested through more formal approaches.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02305-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Epidemiology of Intracranial Neoplasms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
Other:	Tatiana Kudrjavcev	Neurologist	NES	ODIR	NINCDS

COOPERATING UNITS (if any) B.W. Christine, M.D., M.P.H., Connecticut State Dept. of Health; J.P. Whisnant, M.D., and R.J. Campbell, M.D., Mayo Clinic; L. Mahalak, M.D., Jackson, MS; A. Heck, M.D., Univ. of TN; R. Simon, M.D., Berkeley, CA; B. Jordan, B.A., Harvard Medical School

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Section has conducted extensive investigations on the descriptive epidemiology of primary intracranial neoplasms using data derived from population-based registries worldwide. Analytic studies were carried out to investigate the relationship between intracranial neoplasms and tumors occurring at other sites. These studies included careful review of tumor nomenclature, disease definitions, and survey strategies.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02307-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Educational Resources in Neurological Epidemiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any)

D. Schoenberg, M.S., Research Epidemiologist, Bethesda, Maryland

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of four videotapes on the principles of neuroepidemiology were produced by the Section. A two-day international conference on neuroepidemiology was held in 1977; a one-day course was held in 1977; a one-day symposium was held in 1979; a three-day course was held in the People's Republic of China in 1980; a one-week course was held in Madrid, Spain in 1981; an international advanced course was held in Florence, Italy in 1981; a three-day symposium will be held in Edinburgh, Scotland in 1981; a one-day symposium will be held in Kyoto, Japan in 1981; and a one-day course is planned for the United States in 1981. A textbook entitled Neurological Epidemiology: Principles and Clinical Applications was published during 1978, and a new international journal entitled Neuroepidemiology was begun in 1982.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02370-04 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

*Racial Differentials in the Prevalence of Major Neurologic Disorders and Surveys in Developing Countries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Bruce S. Schoenberg	Chief	NES	ODIR	NINCDS
	Dallas Anderson	Survey Statistician	OBFS	OD	NINCDS

COOPERATING UNITS (if any) OBFS, OD, NINCDS; A. Haerer, M.D., Univ. of Mississippi; U.S. Bureau of the Census; C.L. Bolis, M.D. (WHO); B.O. Osuntokun, M.D. (Nigeria); F. Garcia-Pedroza, M.D. (Mexico); Wang Chung-cheng, M.D.(People's Republic of China); E. Bharucha, M.D. (India); M.C. Gutierrez del Olmo, M.D., & A. Portera-Sanchez, M.D. (Spain); J. Cabrera,M.D.(Peru);P.Ponce,M.D.(Venezuela),& Dr.M.Cruz(Ecuador)

LAB/BRANCH
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SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.5	5.5	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to accurately document possible racial differentials in the prevalence of major neurologic disorders by surveying an entire county, with a biracial population of approximately 25,000. The disorders investigated include cerebral palsy, dementia, psychomotor delay, epilepsy, Parkinson's disease, essential tremor, and cerebrovascular disease.

In addition, research protocols for neuroepidemiologic studies in developing countries have been prepared for Nigeria, Mexico, the People's Republic of China, Peru, Spain, Ecuador, and Venezuela. Pilot investigations have been successfully carried out in Nigeria and the People's Republic of China.

*[Former title: Racial Differentials in the Prevalence of Major Neurologic Disorders.]

25 - ODIR/IRP (NES)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02423-03 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Data Resources for Neuroepidemiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any) F. Clifford Rose, M.B., F.R.C.P., B. Benjamin, Ph.D., S. Haberman, M.A., F.I.A., and R. Capildeo, M.B., B.S., Charing Cross Neuroepidemiology Unit, London, England; W. Sibley, M.D., Univ. of Arizona, Tucson, Arizona.

LAB/BRANCH
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SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To develop 1) a registry of hospitalized patients with neurologic diseases in a well-defined population of 3.5 million people, and 2) resources for case-control studies of multiple sclerosis using uniform methods of data collection.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02424-03 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Standardized Nomenclature and Coding of Neurologic Diseases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Bruce S. Schoenberg Chief NES ODIR NINCDS

COOPERATING UNITS (if any) L. Kurland, M.D., Mayo Clinic, Rochester, MN; J.F. Kurtzke, M.D., Georgetown Univ., Washington, D.C.; F. Clifford Rose, M.B., F.R.C.P., B. Benjamin, Ph.D., S. Haberman, M.A., F.I.A., and R. Capildeo, M.B., B.S., Charing Cross Neuroepidemiology Unit, London, England; L. Schut, M.D., Minneapolis, MN; and K. Kondo, M.D., Tokyo, Japan

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	2.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To develop an internationally acceptable standard of nomenclature, classification, and coding of neurologic disorders.

PHS-6040
(Rev. 2-81)

TAB 7.B -- NEUROTOXICOLOGY SECTION, ODIR -- NTS/ODIR

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Neurotoxicology Section, ODIR
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
for period October 1, 1981 through September 30, 1982
Neurotoxicology Section
Office of the Director
Intramural Research Program
National Institute of Neurological and Communicative
Disorders and Stroke
Richard L. Irwin, Chief

SUMMARY

In Vitro Studies of Erythrosin B Neurotoxicity

We have previously demonstrated that erythrosin B (tetraiodofluorescein, U.S.F.D. & C. Red No. 3), a commonly-used artificial food and drug color: 1) blocks synaptosomal uptake of dopamine; 2) inhibits ATP catalysis by brain Na,K-ATPase; 3) inhibits the high affinity binding of the cardiac glycoside, ouabain, to brain Na,K-ATPase; and 4) binds to rat brain cortical membranes. We have recently demonstrated that subcellular distributions of [^{3}H]ouabain and [^{14}C]erythrosin B binding in fractionated cortical tissue preparations are equivalent and parallel ATPase activity. The dissimilar response of [^{3}H]ouabain binding and [^{14}C]erythrosin B binding to changes in tissue preparation, incubation temperature, and partial solubilization of binding sites by deoxycholate (DOC) suggests two separate binding sites for erythrosin B and ouabain to rat cortical membranes. Although characterization of a model for a classical receptor for erythrosin is incomplete, current evidence indicates that in crude cortical membrane preparations specific binding of erythrosin B is composed of a saturable and a non-saturable component. Whether the non-saturable component is removable without loss of enzyme activity and [^{14}C] erythrosin B binding remains to be clarified. Recent studies demonstrate that the potency and specificity of the non-competitive inhibition of [^{3}H]ouabain binding to Na,K-ATPase and ATP catalysis is influenced by glycoside concentration, monovalent cation concentration, and incubation time. Preincubation of the tissue with erythrosin B and other variations in assay conditions result in the inhibition of not only high affinity ouabain binding to Na,K-ATPase but also low affinity ouabain binding and the catalytic activity of non-sodium dependent ATPases.

The cellular toxicity of erythrosin B and some structural analogs were examined for their ability to inhibit the growth of neurites of chick dorsal root ganglia in culture. Inhibition of NGF-stimulated differentiation is due, in part, to the direct photo-oxidation of nerve growth factor by erythrosin B and Rose Bengal. However, there are other light-insensitive actions of erythrosin on both neurons and fibroblasts which were also observed in these studies.

In collaboration with the Department of Biochemistry, University of Miami Medical School, we have shown that the calcium-translocating ATPase of muscle sarcoplasmic reticulum is inhibited by erythrosin B with an IC_{50} of 1μm. The dye also inhibits calcium transport (IC_{50} = 500nM) and binds to a specific site with a K_d of 300 nM. These effects are light-insensitive and distinct from any glycoside-like effect since this tissue contains no enzyme that is sensitive to ouabain, nor specific glycoside binding sites. Blue dextran inhibits dye binding suggesting that the dye binding site is near to but distinct from the nucleotide binding site.

In Vivo Studies on Erythrosin B Neurotoxicity

In chronically implanted, free-moving rats and in lightly anesthetized animals, fluorescein and a series of halogenated fluorescein derivatives were infused in an anterograde manner through the common carotid artery. The distribution patterns of these dyes through the brain and other body organs were visualized and analyzed macro- and microscopically as a function of dose and time after injection. These analyses were performed for fluorescein, erythrosin B, eosin B, eosin Y, rhodamine B, phloxine B, rose bengal, and merbromin.

Investigations of Variable Sensitivity to Neurotoxins

Variation in nervous system anatomy, function, and/or neurochemistry can be used not only to identify individuals who may be predisposed to increased risk from neurotoxic insult but also as a research tool useful in elucidating mechanisms of action of neurotoxins. The Neurotoxicology Section has been investigating the neurotoxic actions of erythrosin B (tetraiodofluorescein, U.S.F.D. & C. Red No. 3) on Na,K-ATPase. In order to elucidate the mechanisms of action of this neurotoxin we have searched for variation in rodent brain Na,K-ATPase. We have found large changes in cortical Na,K-ATPase catalytic activity during neonatal development and aging as well as both quantitative and qualitative variation in ouabain binding during development. Arrhenius plots indicate age-dependent variation in the lipid environment surrounding Na,K-ATPase of cortical membranes. The development of myelin and diverse lipid composition are both probable sources of the age variation in brain Na,K-ATPase we have observed. We have also found reduced ATPase catalytic activity in cortical tissue preparations from rat brains of LA/N cp/cp rats, which have an autosomal recessive mutation for obesity. This difference is consistent with the reduced red blood cell Na,K-ATPase activity found in idiopathically obese humans. These age-dependent and genotypic variations in brain Na,K-ATPase are being examined further with emphasis on what this diversity in Na,K-ATPase can reveal about the interactions of erythrosin B with Na,K-ATPase.

Chromaffin Granules and Chromaffin Cells

The chromaffin cell provides a well-studied system for investigating molecular and cell-surface mediated mechanisms of neurotoxin action. Since several neurotoxins of interest to neurology are divalent cations (lead, manganese, copper) and since storage granules, such as chromaffin granules, synaptic vesicles, and platelet granules contain high concentrations of calcium, these preparations have been investigated to determine the effect of toxic cations on calcium storage and calcium-mediated processes of fusion and exocytosis.

Nuclear magnetic resonance studies performed in collaboration with Dr. J.L. Costa, CN, NIMH, demonstrate that at physiological osmotic pressures the catecholamine and AZP are unhindered. However, if the granules are dehydrated in high sucrose, the spectra resemble the gel-like mobility pattern seen in pig platelet granules.

Chromaffin granules will aggregate and fuse in the presence of calcium. This reaction is independent of ATP and is not inhibited by a phosphodiesterase inhibitor, theophylline. Rapid freeze fracture electron microscopic studies demonstrate that membrane-associated particles move prior to fusion. Aggregation studies by light scattering readout from a stopped-flow apparatus have been extended using fluorescent energy transfer.

Results have provided the first demonstration of the fluid mosaic structure of the membrane of a subcellular organelle. Granule-granule recognition and aggregation is mediated by protruding proteins; however, labelling studies indicate that these proteins contain no free sulfhydryls or that no significant detectable energy transfer occurs because of the geometry of these particles.

Hormones and Central Neurotransmitter Function

We have shown that exposure of male rats to elevated levels of 17ß-estradiol for 6 days produced changes in the striatum. The density of the striatal dopamine receptors was increased, as were the behaviors associated with these receptors. Estrogen administration increased the density of the striatal dopamine receptors, increased the stereotype behavior after dopamine agonist administration, increased catalepsy after dopamine antagonist administration, and increased rotation after dopamine agonist administration in unilaterally lesioned rats. Estrogen had no effect in vitro, demonstrating a specific in vivo response to the drug. The change in receptors is specific since other receptors in the striatum are not altered and dopamine receptors in other areas of the rat brain are not increased in density. The increase in striatal dopamine receptor density is to one specific population of receptors since the increase can be prevented by prior destruction of the neuronal cells originating in the striatum by the neurotoxin, 6-hydroxydopamine. The biochemical response to estrogen is similar in male and long-term ovariectomized female rats. The behavioral responses in the male and female rats are quite different. The biochemical effects of estrogen can be prevented by hypophysectomy, suggesting a pituitary factor such as prolactin may be responsible. The increase in the density of striatal dopamine receptors, produced by the chronic administration and acute withdrawal of haloperidol, can also be attenuated by hypophysectomy, again suggesting the importance of a pituitary factor in the development of an increase in receptor density. Accordingly, prolactin by itself in normal male and hypophysectomized male rats can increase the density of the striatal dopamine receptors. These studies possess relevance in neurologic, psychiatric, and neuroendocrinologic disorders.

Neurobehavioral Analysis of Psychotropic Drugs

We have analyzed neurochemical codes of cataleptic states, which are behaviorally similar to opiate and neuroleptic catalepsy, and their specific relationships to other psychotropic-drug-induced behaviors, including stereotypy, locomotor hyperactivity, distinct epileptic seizures, coma, and death. To this end, the Na-K ATPase inhibitor ouabain was microinjected into the ventricular system, hippocampal formation and/or neocortex. Finally, the contrasting reflex mechanisms underlying opiate versus neuroleptic catalepsy were studied. To that end, a new technique of labyrinthectomy was developed in and applied to rats.

Exocytosis Modelling: Kinetics of Membrane Aggregation and Fusion

Methods have been developed to label the granule membrane with fluorescent lipids, allowing studies of the kinetics of the fusion of the bilayers of these particles. A multichannel, computer controlled stopped-flow rapid mixing spectrometer has been constructed in collaboration with Dr. Paul Smith and Mr. Carter Gibson, of BEIB, to study these reactions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02264-06 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Animal Models of Neurological Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Sally M. Anderson	Expert	NTS	NINCDS
Other:	Roger Weir	Guest Worker	NTS	NINCDS

COOPERATING UNITS (if any)

NONE

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.25	1.0	1.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is investigation of basic mechanisms associated with neurological disease using animal models that have been produced by exposure to synthetic or naturally occurring neurotoxins. The interactions of various toxins with neurotransmitters and hormones in the CNS have provided the focus for combined behavioral and neurochemical studies emphasizing basic mechanisms of action of proposed neurotoxins. Two major interests of this project are: 1) to define populations of individuals that may be at increased risk to neurological disease resulting from exposure to neurotoxins and 2) to use naturally occurring variability in central nervous system function, anatomy and/or neurochemistry, to elucidate mechanisms of actions of neurotoxins. The primary emphases this year have been: 1) the interaction of artificial food colors with neuronal membranes and neurotransmission; 2) the investigation of genetic and age variation in brain Na,K-ATPase (an enzyme previously demonstrated to be inhibited by artificial food color); and 3) neuronal interactions between neuropeptides and dopamine in the basal ganglia.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02451-02 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cellular and Molecular Approaches to Neurotoxicology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Stephen J. Morris	Expert Consultant	NTS	NINCDS
Others:	Bibie M. Chronwall	Fogarty Fellow	SNB	NINCDS
	Jonathan L. Costa	Staff Physician	CNB	NIMH
	Robert Blumenthal	Section Chief	LTB	NCI
	Duncan H. Haynes	Assoc. Prof., Pharmacology, Univ. of Miami		
	J. David Robertson	Chairman, Anatomy, Duke University		
	Joseph M. Costello	Assoc. Professor, Anatomy, Duke University		
	Thomas M. Jovin	Chairman, Molecular Biology, Max Planck Inst.		
	Victor P. Whittaker	Chairman, Neurochemistry, Max Planck Inst.		
	Thomas C. Sudhof	Graduate Student, Neurochem., Max Planck Inst.		
	Ward F. Odenwald	Microbiologist	NTS	NINCDS
	Michael K. Ho	Biologist	NTS	NINCDS

COOPERATING UNITS (if any)
University of Miami Medical School, Miami, FL 33101; Duke University Medical School, Durham, NC 27706; Max Planck Institute for Biophysical Chemistry, D-3400 Goettingen, F.R. Germany; SNB, NINCDS, CNB, NIMH

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.3	1.7	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several in vitro systems were explored for their applicability to the testing of (suspected) neurotoxic substances, such as Erythrosin B (FD and C Red 3) (EB) an artificial halogenated fluorescein derivative. The dye can be used to trace solubulization and partial purification of rat brain cortex ATPase. It also inhibits ATPase and calcium transport activity of rabbit muscle sarcoplasmic reticulum. EB inhibits axonal outgrowth from chick dorsal root explants by photo-oxidizing NGF. General in vitro toxic effects are also seen.

Storage and release of catecholamines from adrenal medullary cells are affected by a variety of heavy metals, partially through interference with calcium-specific mechanisms involved in release of the neurotransmitter. The calcium-promoted fusion of isolated chromaffin granules, and its inhibition by various heavy metals, is being studied as a model process for exocytotic release of catecholamines in vivo. The kinetics of calcium-promoted aggregation and fusion of the granules have been studied using fluorescence energy transfer techniques.

32 - ODIR/IRP (NTS)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02452-02 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hormones and Central Neurotransmitter Function

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Robert E. Hruska	Senior Staff Fellow	NTS	NINCDS
Others:	Marc De Ryck	Visiting Fellow	NTS	NINCDS
	Roger Weir	Guest Worker	NTS	NINCDS
	Karen Pitman	Biologist	NTS	NINCDS
	Diane Bradley	Biological Aid	NTS	NINCDS
	Lynn Ludmer	Biological Aid	NTS	NINCDS

COOPERATING UNITS (if any)

NONE

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.7	0.9	1.8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Hormones, such as estrogen or prolactin, affect cerebral neurotransmitter receptors. Estrogen increases the following: (1) the density of striatal dopamine (DA)receptors; (2) stereotypy induced by DA agonists; (3) catalepsy produced by a DA antagonist; and (4) DA agonist-induced rotation in unilaterally lesioned rats. The increase in DA receptor density is specific and restricted to one population. In the striatum, this increase is prevented by hypophysectomy, suggesting involvement of a pituitary factor. The increase in DA receptor density after chronic haloperidol is also attenuated by hypophysectomy, again suggesting a pituitary factor, such as prolactin, which by itself increases the density of striatal DA receptors.

We have also analyzed neurochemical codes of cataleptic states, behaviorally similar to opiate and neuroleptic catalepsy, and their experimental relationship to other psychotropic-drug-induced behaviors, including stereotypy, locomotor hyperactivity, distinct epileptic seizures, coma, and death. Other experiments show that contrasting reflex mechanisms (i.e., vestibular controls) underlie opiate vs. neuroleptic catalepsy. These findings may be relevant to neurologic, psychiatric, neuroendocrinologic disorders, and drug-induced side-effects.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02525-01 ODIR

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Exocytosis Modelling: Kinetics of Membrane Aggregation and Fusion

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Stephen J. Morris	Expert Consultant	NTS	NINCDS
Others:	Paul D. Smith	Visiting Scientist	BEIB	DRS
	Carter G. Gibson	Electronics Engineer	BEIB	DRS
	Duncan H. Haynes	Assoc. Prof., Pharmacology Department, Univ. of Miami Medical School		
	Alan Malvino	Technician, Pharmacology Department, Univ. of Miami Medical School		
	Orhan K. Oz	Biologist	NTS	NINCDS

COOPERATING UNITS (if any)

Department of Pharmacology, University of Miami Medical School

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.5	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Neurotransmitter release from synapses and neurosecretory cells involves exocytosis: the fusion of the synaptic vesicle membrane with the cell plasma membrane.

The kinetics of the reactions involved in membrane fusion in a model system consisting of sonicated phospholipid vesicles are being studied using a computer-controlled multisignal stopped-flow rapid mixing apparatus.

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(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02319-05 ODIR

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analytic Electron Microscopy in Neurochemistry

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ellen K. Silbergeld	Chief	NTS	NINCDS
Other:	C. Fiori	Physicist	BEIB	NIH

COOPERATING UNITS (if any) Department of Neuropathology, Johns Hopkins Hospital, Baltimore MD; Department of Neurology, Tufts Medical School, Boston MA; Department of Neurology, Univ. of Michigan Medical School, Ann Arbor, MI; BEIB, NIH

LAB/BRANCH

Office of the Director, Intramural Research Program

SECTION

Neurotoxicology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been discontinued.

PHS-6040
(Rev. 2-81)

TAB 7.C -- INSTRUMENTATION & COMPUTERS SECTION -- ICS/ODIR

ANNUAL REPORT

October 1, 1981 - September 30, 1982

Instrumentation and Computers Section
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report of Instrumentation and Computer Section

National Institute of Neurological and Communicative Disorders and Stroke

October 1, 1981 - September 30, 1982

The Instrumentation and Computer Section provides technical support for investigators by (1) assessing the instrumentation and computer needs of the investigator; (2) designing, developing and constructing special-purpose electronic and mechanical instrumentation and systems not commercially available; (3) designing, specifying and managing laboratory computer systems for data acquisition and processing.

Additional services provided by the Section include consultation on measurement techniques, signal processing, noise and electro-magnetic interference in data measurement systems, and equipment purchases. Several formal and informal courses for investigators are taught by Section personnel; topics include electrical circuit theory, operational amplifier applications, digital logic design, and computer applications.

Due to manpower limitations and economic considerations, the Section is unable to provide the following services: repair of commercial instruments, duplication of off-the-shelf commercially available equipment, and fabrication of non-instrument items (shelves, bookcases, etc.).

When an investigator requires the services of the Section, he first meets with the Section Chief and other personnel as needed to discuss his requirements. On the basis of this meeting, a decision is made as to whether ICS (Instrumentation and Computer Section) will take on the project. If a commercially produced instrument will satisfy the investigator's requirements, he is advised to purchase it. If custom instrumentation is needed, ICS will accept the project unless we lack the appropriate expertise, or our current work backlog is excessive. In these cases the project may be contracted to a private firm, or the investigator may be directed to the Biomedical Engineering and Instrumentation Branch (BEIB).

When the Section Chief or the Assistant to the Chief agree to accept a project, the investigator submits a standard work request form (available from ICS), signed by his Lab Chief. This form will state the nature of the instrument or service requested, and will contain as many details and specifications as the investigator can provide.

The project is then assigned to an engineer, who will confer with the investigator to formulate a set of engineering specifications and a timetable and cost estimate for the project. The ICS does not charge for services, but the investigator will be billed for the cost of the components used. Upon delivery of the completed instrument, a memo is sent to the investigator listing the component costs and asking permission to have the Administrative Officer transfer funds from his CAN to the Section's CAN.

INSTRUMENTATION

The Section has a staff of six engineers and six technicians to design, develop and fabricate electronic and mechanical instruments. The major effort is in the production of electronic instruments for basic neurophysiological research, and for clinical studies involving affective disorders. The following are brief descriptions of representative projects, chosen from a total of 310 projects completed this year.

(1) Patient Activity Monitoring System. The Section has continued to develop the Patient Activity Monitor (PAM) and the support hardware and software which forms the system. The standard PAM, which provides 64 hours of data at 15 minute intervals, was redesigned to use batteries which have 18 months capacity. The software has been expanded, and a provision has been made to acquire and store data from a commercially available temperature monitor which utilizes the same data storage principal as the PAM.

A program was written to allow activity or temperature data to be stored in continuous files of unlimited length; this simplifies long-term data analysis. Numerous other programs, including automatic sleep recognition and various graphical data presentation techniques, were added this year. An extensive users guide to the PAM software was written.

The major hardware advance this year has been the development of a PAM to replace the hybrid monitor. The hybrid, which stores over 10 days of data and is much smaller than the standard PAM, was based on the technology of connecting integrated circuit dies to thick-film printed substrates by microminiature wire bonds. These hybrid PAMs were fabricated by a private contractor. Unfortunately, they proved to be very failure-prone, and the devices cannot be repaired. We have abandoned this technology, and are completing development of a PAM with all the characteristics of the hybrid, but much more reliable and less expensive. It is easily fabricated, using pre-tested parts, and can be repaired if necessary. It will become our standard device, and will eventually replace all the older PAMs.

The PAM is being evaluated for use in determining sleep stages, without taking sleep EEG recordings. PAMs are placed on the head, trunk, and wrist or ankle; algorithms are being developed to determine sleep stage as a function of relative activity at the three sites. If successful, this technique would greatly expand the possibilities for outpatient sleep research.

(2) EEG Amplifier System. A 32-channel EEG amplifier system was designed for use in several ongoing research projects involving topographic brain mapping. The design incorporates several new electrical components which permit construction of a compact, low cost-per-channel unit. The system consists of a preamplifier, located next to the subject, joined to a main amplifier by a flat cable. The signal gain in the preamplifier is 1,000 and, in the main amplifier, 30, for an overall gain of 30,000. An important part of the amplifier design is the filter section. The filters were designed to prevent aliasing errors when the signal is digitized; to eliminate any phase distortion in the passband region that would interfere with time-series average evoked response analysis; and to have a good step response, to minimize "ringing" resulting from stimulus artifacts. The design also includes a sample-and-hold module on each channel to prevent any "skewing" errors associated with A/D conversion.

(3) Computer-Controlled Trapezoid Generator. A torque motor position control system was previously developed by ICS for research on the mechanisms which produce the tremor of Parkinson's disease and also for general neuromuscular research. A signal with a trapezoid timecourse which could be synchronized with the data collection computer was thought to be a very useful command input to the torque motor system. To satisfy this need, a precision, computer-controlled trapezoid generator has been developed. A PDP-11 minicomputer loads the trapezoid parameters (up time, hold time, down time, and amplitude and polarity) into the generator via a parallel digital interface. A fifth parameter from the computer starts the trapezoid waveform and sets the duration of the control signals for the torque motor system. By allowing synchronization between stimulus and computer data acquisition, this trapezoid generator has greatly facilitated use of the position control system.

(4) Tissue Culture Voltage Clamp System. A voltage clamp system has been developed for investigating the membrane properties of electrically and chemically excitable tissue culture cells. This low voltage system was designed for use with two high impedance glass microelectrodes to clamp slow-to-medium speed neuronal voltage changes but not action potentials. Two identical headstage amplifiers are provided so that after electrode placement in the cell, either electrode may be used to measure the membrane potential. These headstage amplifiers also may be used as constant current sources for current clamping experiments. A dual sensitivity/speed virtual ground current monitor is also provided.

(5) Discriminator and Iontophoresis Systems. The ICS amplitude/time window discriminator system continues to be an important signal processing tool in neurophysiological studies. The versatility of this system has been increased and the design simplified by implementing the circuitry with CMOS logic. Six of these new discriminator systems were completed this year and two modified units for processing post-synaptic potentials are under construction. Although micropressure ejection of drugs from multibarreled pipettes has become, in many cases, the preferred method of drug application, the use of microiontophoresis is still widely used. Four of the ICS 5-channel iontophoresis systems are presently nearing completion and will be used in neuropharmacological studies in the IRP.

(6) Data Acquisition System for Isolation Rooms. Two isolation rooms are being designed to permit the study of biological rhythms and the cyclic nature of certain mental illnesses. Each room will be occupied by one human subject who will be isolated from all time cues. ICS is designing a computerized data acquisition system for these rooms so that activity and temperature data can be periodically recorded. Recording mood self-ratings and limited subject-staff communications will be provided by special touch-input CRT terminals.

(7) Resistance Monitor and Shutter Controller. In order to view a freeze-fractured sample of tissue with an electron microscope with greater resolution, a thin layer of metal is first deposited on the sample. The resulting resolution will be dependent on the amount of metal deposited and the length of exposure time of the sample to the heat of the ion gun. A controller has been developed that monitors the amount of metal being emitted by the ion gun by measurement of resistance changes as metal is being deposited between two terminals separated by a fixed length and width of non-conducting fiberglass board. A shutter, which can be opened and closed at variable resistance limits, is used to control the amount of material deposited and to make the exposure time of the sample to the heat of the ion gun as short as possible.

(8) Visual Evoked Response Stimulus System. A visual evoked response stimulus system has been built, that will randomly select one of the eight 35mm slide images and project it on to a 35cm X 50cm opaque screen. The projection system uses a very fast electromechanical shutter (2.3 msec. opening time) for a fast rise time in presenting the image. The slides are mounted on a circular disc, which is rotated by a direct-drive stepper motor. The maximum random access time for any slide is 125 msec. The stepper motor is controlled by a special-purpose processor that can be linked to either a computer or a terminal through a standard RS232 serial interface.

(9) Neuro PET Scanner Chair and Gantry Controller. A controller is being designed for the Neuro PET Scanner which was developed by NINCDS in conjunction with BEIB. This controller will facilitate the positioning of the patient's head into the scanner through control of an electromechanical chair. This device will insert the patient's head a fixed distance into the aperture of the scanner from a predetermined setup position. The controller will provide a digital readout of the patient's position and will include various safety stops to prevent collision of the chair and the gantry.

(10) Programmable Infusion Pump. A microprocessor-based instrument was developed to control a motor driven syringe platform (infusion pump). The pump is used to maintain a constant arterial concentration of infused substances during absorption studies with laboratory animals. The pump delivers an initial bolus followed by an exponentially decreasing infusion pumping rate. A calibration mode is available for generating syringe and motor calibration coefficient. Initially the instrument prompts the operator for pumping schedule parameters, calculates necessary variables, and executes the pumping schedule. An on-line pumping schedule listing is available or a pre-pumping listing of the programmed schedule may be requested. The listing provides the pumping rate/volume per delta time for the infusion schedule and the total volume delivered.

(11) 4-Arm Radial Rat Maze. An elevated multi-level 4-arm radial rat maze is being constructed and instrumented to assess the effects of neuropeptides on learning, memory, and perception in experimental animals. Audible and/or visual cues will be presented at the end of a randomly selected arm. The path of the animal is monitored by detectors located at selected positions throughout the maze. When an animal traverses the proper path to the cues, a programmable liquid reinforcement will be dispensed. At the end of the testing period, statistical data will be printed regarding the animal's performance. An 8-bit microprocessor single board computer is used to monitor and control the maze and perform the necessary statistical calculations.

COMPUTERS

The Instrumentation and Computer Section (ICS) continues to support the use of the computer as a laboratory instrument. Small computers are used in the individual laboratories for on-line, real-time interaction, process control and data acquisition. ICS maintains support computers in Buildings 10 and 36. These systems provide means for program preparation, bulk storage, printing and plotting, and mathematical and statistical processing. Experimental data may be transmitted from the laboratory computers, via these systems, to the DCRT facilities for further processing. The support computers also serve to develop prototype

systems and to test the feasibility of the use of a computer in specific laboratory applications. The latter capability allows an investigator, once he determines that the computer will do the job, to purchase an efficient system at minimal cost. The Section also maintains an image processing system, described below.

The Section provides software support for the individual investigators. A library of procedures has been developed that is tailored to the needs of the Intramural Program. Individual training is available for investigators with no prior experience in using or programming the computer. Computer specialists are available for consultation in all areas of computer use, programming, interfacing, real-time applications, time series analysis, data presentation, systems configuration and computer procurement. Although ICS does not provide an applications programming service, systems have been developed in collaboration with individual laboratories. Examples are included in the list of computer projects.

Program maintenance is an important function of the Section. Programs used in a real-time interactive laboratory research environment often produce new information which calls for modification of the program before the next experiment. In addition to the software library and research related projects developed by ICS, much work is caused by the turnover of scientific and support personnel. Many systems developed by these persons prove useful to the laboratory. After they leave, maintenance of such systems becomes the responsibility of ICS. Structured programming techniques and standardization on PASCAL have enabled the Section to provide these services without an increase in personnel. There are currently more than 50 minicomputers in the Intramural Research Program.

The Section also maintains a microprocessor development system for software and hardware development of microprocessor-based instrumentation at both the chip level and the single board computer level. The system currently supports three common microprocessors; one 16-bit processor, and two 8-bit processors. Various utility programs and two high level language compilers are available (FORTRAN and PLM) for application programming.

The support computer in Building 36 was upgraded this year, and with the acquisition of two laboratory systems for program development, much of the burden on this facility has been somewhat relieved. However, increasingly sophisticated mathematical algorithms are being developed in the areas of image processing, cell membrane analysis, and digital signal processing. These techniques require an increasing amount of processor time, and the existing single user systems are not the most cost effective method of handling these problems.

A Digital Equipment Corp. VAX-750 32-bit computer has been installed in Bldg. 36. Space for this facility is furnished by the Laboratory of Cerebral Metabolism, NIMH. This computer processes mathematical data more efficiently than any of the existing 16-bit computers and has a time shared, virtual memory operating system. It has a compatibility mode in which programs written on the existing computers will run with little or no modification. Programs may be written and compiled on this system to be run on the laboratory computers. The two existing image processing systems will be linked directly to this computer, via a high-speed communication linkage. Future plans call for connecting laboratory computers to the facility and developing a true distributed network. This will provide increased capability for the laboratory satellite, at less cost to the user.

Image Processing System

The Instrumentation and Computer Section maintains a general purpose image processing system. This system consists of a high-speed rotating drum scanner, an image array processor and display, and a PDP-11/60 computer. The drum scanner can digitize transparencies up to 10x10 inches with spatial resolution of 12.5 microns. The image array processor can simultaneously store, display and manipulate up to three 512x512 digitized images. Images may be compared, superimposed, translated, zoomed or color coded at video rates. Images to be processed may be obtained by scanning autoradiographs, x-ray film, or photographic negatives, or by using previously digitized images generated by CAT or ECAT scanners. A camera station is being added this year.

An interactive, menu-driven, software system provides an extensive and expandable repertoire of basic image processing and input/output functions. Special purpose functions can be developed to meet specific user requirements. The facility is useful for numerous applications involving evaluation and quantification of biomedical images. Two applications, however, are primary analysis of two-dimensional electrophoresis gels and analysis of autoradiographs of brain or tissue sections.

The autoradiographs are used for measurements of glucose utilization in brain tissue using the Sokoloff deoxyglucose method of glucose substitution. Analysis of the autoradiographs involves displaying the digitized image on a TV monitor and outlining areas of interest. The average optical density is then computed and automatically converted to glucose utilization. Glucose utilization of brain regions as small as 100 microns in diameter can be computed. A color coded glucose utilization map may also be produced.

Measurement of amino acid concentrations can be made using two-dimensional electrophoresis gels. The gels, which have been prepared by the appropriate stain and fixer, are photographed; or if radioisotopes are used, an autoradiograph is obtained. The film is scanned and digitized into an array of optical density within a defined boundary. A test gel may be compared with a standard gel using the image array processor to determine the presence or absence of a particular substance.

Additional examples of computer projects include:

(1) Fine Motor Control Evaluation Project. Programs have been developed for evaluating fine motor control movements in Parkinson patients using a peripheral device called the Bit-Pad I (Summographics Corp.). It consists of a magnetostrictive surface sensitive to the position of a pen-like stylus. The device transmits the position of the stylus through a standard computer interface. The program determines, over a series of trials, how well the subject can move the stylus through a series of positions on a pattern, in a connect-the-dots fashion. Each trial consists of at least five successive repetitions. Evaluation is based upon speed and accuracy. The reaction time of the subject is measured at the start of each trial; it is thought that this can be related to the number of positions in the pattern that the subject must subsequently traverse. The test should be a sensitive indicator of the amount of fine-motor dysfunction in Parkinson patients.

(2) Cell Culture Analysis. This system is designed to provide an on-line analysis of tissue culture neurons. The first phase, to study the excitatory or inhibitory post-synaptic potentials of these cells, has been completed. A unique feature of this system is the on-line control of artifacts introduced by the measurement system and the properties of tissues in culture and to control the threshold levels and amplification level as the experiment is in progress. Visual displays of amplitude, integral and latency are available, as well as averaged evoked response. In addition, on-line monitoring of post-synaptic potentials elicited by stimuli presented in pairs or in trains of pulses are available. The system also studies spontaneously occurring miniature potentials. This system is being extended to allow analysis of the cells by other techniques such as voltage clamping and the iontophoretic injection of neuroactive substances on the surface of the cell.

(3) Neurophysiological Data Analysis System. This system was initially developed for the Laboratory of Neurophysiology, NIMH, and has found widespread use. It is a versatile system for the collection and analysis of neurophysiological data, such as cortical unit events, lever position, EMG, etc., with behavioral events, and allows the presentation of this data in its relation to any time locked variable. The data are displayed as rasters and histograms of the neural events, centered on behavioral criteria, with the ability to mark selected events, and also the analog sweeps associated with these trials. Extentions are being made to this system to enhance its utility; these include the ability to select groups of trials within a unit, the selective deletion of sweeps, and the shifting of individual rasters in time. In addition, the individual trials may be sorted on a number of variables included in the data. A time window may be selected and a sort made on the pulse count (neural events) or selected criteria from the analog data such as the integral, slope, maximum amplitude or the latency to the first derivative.

ENGINEERING, COMPUTER AND FABRICATION SERVICES

This table shows the distribution of the Section's workload among the various laboratories and branches.

LABORATORY OR BRANCH	HOURS	PERCENT
Clinical Science, NIMH	2543	9.49
Neurophysiology, NINCDS	2511	9.37
Neurophysiology, NIMH	2475	9.23
Biological Psychiatry, NIMH	2428	9.06
Clinical Psychobiology, NIMH	1902	7.09
Cerebral Metabolism, NIMH	1738	6.48
General and Comparative Biochemistry, NIMH	1541	5.75
Biophysics, NINCDS	1403	5.23
Neuropathology and Neuroanatomical Sciences, NINCDS	1312	4.89
Molecular Biology, NINCDS	1096	4.09
Neurochemistry, NINCDS	1012	3.77
Surgical Neurology, NINCDS	987	3.68
Experimental Therapeutics, NINCDS	710	2.65
Neuropsychology, NIMH	594	2.22
Psychology and Psychopathology, NIMH	509	1.90
Adult Psychiatry, NIMH	438	1.63
Molecular Genetics, NINCDS	359	1.34
Infectious Diseases, NINCDS	270	1.01
Neurochemistry, NIMH	175	.65
Brain Evolution and Behavior, NIMH	159	.59
Neuroimmunology, NINCDS	158	.59
Clinical Neurosciences, NINCDS	150	.56
Neural Control, NINCDS	121	.45
Central Nervous System Studies, NINCDS	101	.38
Other Laboratories and Branches, NIMH	98	.37
NIMH (Total)	14,600	54.45
NINCDS (Total)	10,190	38.01
NICHD (Total)*	2,019	7.54
	26,809	100.00

*NICHD loans the Section one position, and is thus entitled to 1700 hours of service.

TAB 8 -- LABORATORY OF BIOPHYSICS -- LB/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Biophysics
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
October 1, 1981 thru September 30, 1982
National Institute of Neurological and Communicative Disorders and Stroke
Laboratory of Biophysics
William J. Adelman, Jr., PhD, Chief

INTRODUCTION

The research program of the Laboratory of Biophysics is concerned with investigating molecular and cellular mechanisms responsible for excitation, membrane potentials, the generation of the nerve impulse, synaptic activity, the biophysical basis for the functioning of simple nervous systems, and the cellular basis for such integrative neural functions as behavior and learning. The laboratory is composed of two units. One of these units operates on a year-round basis at the Marine Biological Laboratory in Woods Hole, Mass. The Woods Hole Unit is composed of 2 sections: the Section on Neural Membranes and the Section on Neural Systems. The Bethesda unit of the laboratory is made up of the Section on Molecular Biophysics.

Acceptance of the idea that excitability in neurons results from the opening and closing of ion-specific membrane channels is widespread among neuroscientists. Much of the evidence that has led to this acceptance has been based on measurements of current flow through these transmembrane channels. These channels have been described in terms of their individual unit conductances or their conductances in ensemble. Therefore, it is now apparent that any rational description of excitable membrane behavior must be consistent with the behavior of single channels both individually and in the large ensembles found in neurons and muscle cells.

One of the major directions of the Laboratory of Biophysics has been to focus attention on channel behavior as the basis for neuronal function and thus logically as the basis for the function of ensembles of neuronal cells or neural systems. The overall program of the Laboratory of Biophysics (LB) has been conceived with this basis in mind. The program, while having its origin, in part, in the 1950's, was broadened in the 1970's by considering that the overall approaches used to study the biophysics of axon and artifical bilayer membranes could be applied to the study of neural systems. The core of this approach has been the adoption of biophysical methods integrated with modern ultrastructural and biochemical approaches to produce an understanding of complicated mechanisms at fundamental levels. The organizational restructuring of LB in 1974 and the eventual establishment of two sections of LB at the Marine Biological Laboratory in 1975 was a direct outcome of this thinking.

At present, one sees this main thread within the individual programs of the three sections of LB. The predominant approach of the Section on Molecular Biophysics is to study individual channels and their unit conductances. This section also studies membrane conductances or the behavior of channels in ensemble. The Section on Neural Membranes predominantly studies membrane conductances with a strong emphasis on structure at resolutions approaching the molecular or atomic level. Both skeletal and cardiac muscle systems are included within this program. The Section on Neural Systems studies mechanisms by which simple neural

systems process information with a major emphasis on learning mechanisms. The Section's main thrust has been cellular electrophysiology with lateral integrations to membrane conductances, microscopic anatomy, integrative behavior and neuronal biochemistry.

Considered as an entity, the Laboratory of Biophysics is now operating over the broadest range of basic interests in neuronal function. The insights gained at the channel level give direction to the membrane studies and the membrane studies give impetus to the neurophysiological and behavioral investigations. These all receive strong input from the Laboratories' investigations in ultrastructure science and biochemistry. These interrelations are not strictly conceptual as methods, techniques, equipment and personnel also develop in parallel and become part of the direction of LB. It is hoped that the following summary of highlights of LB's recent accomplishments give evidence that this integrative approach is fruitful.

Section on Neural Membranes.

The Section on Neural Membranes uses modern electrophysiological, electron optical, mathematical biophysical, and computer science techniques to investigate the function and structure of neural cells and tissues at limits approaching the molecular level. The general approach is to examine mechanisms that underlie all neural function. Emphasis is placed on membrane ionic channel structure and function. Model systems are derived, tested and used to simulate neuronal function under a variety of natural and experimental conditions. Subcellular structures supportive of axoplasmic transport and membrane ionic channel formation are sought. The physical mechanisms involving the structures of muscle and nerve responsible for contraction and mechanoelectrical transduction is probed and these are related to both the biochemical and structural elements underlying these mechanisms.

It has been clear for many years that electrical excitability involves a mechanism whereby ionic channels in the neuronal membrane make transitions from normally closed states to open states and vice versa. These transitions occur in time in a manner that is dependent on the membrane potential. The measurable phenomena (conductance, charge transfer, flux, etc.) are kinetic in the sense that their time and spatial variations are measurable functions of voltage. These kinetics are usually considered to be the result of channel gating mechanisms. "Gating" is descriptive of the manner and form of opening and closing of the channel gates, accessible traffic through the opening being limited to open times, the characteristics of the unit channels and the nature of the charge carriers. To a large extent, the study of voltage-dependent channel gating has been a major theme in LB.

The Section on Neural Membranes carried on several "gating" investigations during the year. One of these studies examined the kinetics of the gating of the sodium channel with regard to the nature of the channel molecular states involved. Abrupt (microsecond) transitions were observed in the sodium conductance during certain voltage clamp steps. Extended "tail" currents also were observed upon repolarization to the holding potential following other specific clamp pulses. These phenomena have been modeled by including an (energetic) excited molecular state in the activation gating kinetics in parallel to the classical Hodgkin-Huxley kinetics.

Another research effort dealt with calcium binding to (and the distribution of) membrane surface sites in the vicinity of the squid axon potassium channel molecule. The calcium binding constant was found to be 30 M^{-1}, much larger than previously thought, and implying a much lower surface potential (-15 mV) in normal sea water than had been imagined. Surface charge appears to be distributed in such a way that its electric field component influences the channel gating charges much more than the ion flux. This finding implies that the ionic channel is separated from the gating charges by $\geq$ 8 Angstrom units on the basis of the Debye (reciprocal) length theory.

The effects of previous membrane voltage history on potassium channel gating was another study carried out by the section. While activation kinetics were found to be delayed by previous hyperpolarization of the membrane in a manner similar to that found originally by Cole and Moore, translation on the time axis of the delayed responses did not result in superposition of these with the control responses. The disparity between delayed and control depolarizing responses occurred during the first few milliseconds of the rising phase of the potassium current. These results could be described by incorporating a time dependence into the rate constant of activation of potassium channel gates in the Hodgkin-Huxley model of the potassium conductance. Since tail currents could be fit with a single exponential (after taking the effects of ion accumulation into account), the lack of superposition of activation kinetics is not attributable to a second population of potassium channels. That is, potassium current kinetics in squid axons can be modeled by a homogeneous channel population.

The influence of channel blockers such as cesium, rubidium and barium on the current-voltage relations of potassium channels was also studied. The results of this study suggested that an external Cs or Rb ion can be swept into a potassium channel both by membrane potential and by external K ions. The binding of these ions to a binding site some distance from the external mouth of the channel was also suggested. While blockage is apparent primarily when the net channel current is inward, a finite probability for either external Cs or Rb to enter the channel mouth when the net channel current is outward was shown to exist. However, such an effect is only apparent when the blocking ion concentration is relatively large.

In keeping with the overall theme of the Section, a method was developed for simulating single channel openings and closings as a basis for predicting excitable membrane voltage changes, particularly the action potential. It was possible to simulate the behavior of a small population of channels under a variety of conditions. This study is important in that it provides support for the general idea that the spatial summation and temporal variation of single channel unit events is the primary basis for electrical activity in nervous tissue.

In a comparative study involving embryonic heart cells, the general problem of spontaneous and rhythmic behavior of excitable cells was investigated. Voltage clamp experiments were run on these cells which showed that atrial cells have a time-dependent potassium ion repolarization current. The currents for these channels are similar to nerve except that the time constants are about 50 times longer than nerve. Perturbations of spontaneous activity in these cells were achieved and these produced results which provided an explanation for the time bifurcation of interrupted cyclic activity. Implications were drawn from these heart cell studies which might be applied to understanding spontaneous activity in nerve.

A major research effort of the Section continued to be the investigation of mechanoelectric transduction mechanisms in squid giant axons. The following similarities in general responses between this preparation and mechanoelectric transducer organs were observed which relate this model system to general transduction mechanisms. The "primary" response to stretch (axon membrane depolarization) corresponds to the "local" or pre-potential response observed from transducer organs. The primary response is graded and dependent on mechanical stimulus parameters as is the local response. The primary response, if large enough, will lead to a membrane threshold response which is regenerative in nature and produce a spike potential. Evidence suggests that nonconventional sodium channels are involved in the primary response to stretch and that conventional potassium channels are involved in the recovering repolarization.

In additional work, emphasis was placed on a detailed description of the viscoelastic and other mechanical properties of the isolated axon preparation. Thus, mechanical transients produced by rapid stretch of the axon were represented in an analog circuit delay line and, with the use of certain Hodgkin-Huxley formulations, a model was established. Computer simulation of stretches applied to the model yielded electrical responses that were similar to experimental observations.

It is now apparent that there is an intimate relationship between the function of membrane channels in excitable tissues and the structure of both the channels themselves and the neurons and muscle cells in which they are found. It is also apparent that the internal structure of neurons, particularly axons, has many functions. Among these are axoplasmic transport and flow. Therefore, one of the major aims of the Section continues to be an investigation of the fine structure of axoplasm, particularly of the neuroplasmic lattice and its relationship to other cytoplasmic components and the axolemmal surface. To this end heavy use has been made of TEM and STEM techniques using the Philips EM400 electron microscope which, because of its "achromatic" electron optical characteristics, is particularly useful for stereographic examination of relatively thick sections (0.1-0.5 μm). Such thick sections are usually only usefully examined in high voltage electron microscopes. Considerable emphasis has been and continues to be placed on determining the effects of the procedures usually required for electron microscopy, that is, fixation, dehydration, embedding and sectioning.

Computer processing of scanning transmission (STEM) video signals and the application of Fourier analytical methods to the video line signals comprising the picture raster continued to be a convenient and objective method for the characterization of periodic structure in many nerve and muscle subcellular arrays. These image enhancement and analytical methods were greatly expanded by adding energy dispersive x-ray analysis (EDAX) and electron energy loss spectroscopy (EELS) capabilities to the EM400 electron microscope. Much effort has gone into generating computer programs so as to make full use of both digital image processing and analytical techniques now being implemented in conjunction with the EM400. All of these methods are being applied to axons and neurons from several different species, both invertebrate and vertebrate. Several different classes of muscle cells are being examined. The structures of both nerve and muscle cells as seen in the electron microscope are being compared with the protein chemistry of their constituents and with suitable light microscopy imaging of these cells while they are active. These studies are beginning to indicate the general lattice array of neurofilaments, neurotubules, cross-bridges, and which of these elements are characteristic of certain classes of neurons and certain species. All of this has been made possible by an integrative approach

involving electron optics, analytical biophysics, electronic and optical engineering and applied mathematics and computer science (primarily programming and systems engineering).

Section on Molecular Biophysics.

The main goal of the Section on Molecular Biophysics is to determine the molecular mechanisms underlying the behavior of membrane ionic channels and of drugs that interact with these channels.

A major theme of the Section this year has been the use of various chemical agents to determine channel properties or to determine the role of the chemical agents themselves. The chemicals used were batrachotoxin (which opens sodium channels), yohimbine and amioderone (which block sodium channels), dipicrylamine (which is a charged hydrophobic molecule), acetylcholine and other cholinergic agonists and partial agonists, TEMPO (a spin label), and bungarotoxin (which blocks acetylcholine channels).

Another major theme was the use of patch clamp both to observe single ionic channels and to allow voltage clamping of small cells.

Previously, the method of radioactive flux measurement was used to determine some of the properties of batrachotoxin-bound sodium channels in neuroblastoma cells. The method of suction pipet voltage clamping now has been used to determine the voltage dependence of these properties and to obtain faster time resolution. It was found that batrachotoxin opens sodium channels because it shifts the activation conductance-voltage curve about 50 mV in the hyperpolarizing direction and also eliminates both fast and slow inactivation. Thus, at the normal resting potential, when batrachotoxin is present, activation is turned on, inactivation is turned off, and the channels are open. It was found that batrachotoxin also caused several changes in the kinetics of the sodium channel. In particular, the activation process was changed to first order and was considerably slowed. A likely explanation for these changes is that the addition of batrachotoxin slows one of the conformational changes which normally occurs during the opening of sodium channels, and that consequently this event becomes rate-limiting.

There are numerous drugs that act to block sodium channels. In order to determine what features of the blocking molecule are important, a large number of analogs of the use-dependent blocking drug, yohimbine, have been synthesized. These analogs were then tested for activity in experiments on voltage clamped squid axons. The use-dependent blocking action of the analogs correlates well with the presence of a negative charge at a particular region of the molecule. Experiments are planned to subject to further tests our tentative conclusion that binding of yohimbine requires a negative charge at the appropriate position.

Amioderone is another drug which has been found to block sodium channels. Interesting features of blocking by this drug are the long delay before the drug acts and the lack of use-dependence. One motivation for studying this drug is that it is now widely used as an antiarrythmic agent.

An important aspect of channel gating is the role of membrane lipids. Dipicrylamine has been incorporated into axonal membranes in order to compare the normal gating current with an analog gating current produced when dipicrylamine dissolved in a membrane is subjected to a strong electric field. The

dipicrylamine gating current was found to be strongly influenced by the presence of chloroform in the membrane, presumably because chloroform changes membrane viscosity. The normal gating current, on the other hand, was not significantly influenced by chloroform. This strongly suggests that channel gating is essentially independent of the lipid environment.

Gating current observations have so far been limited to the sodium channel. It has not been possible to observe potassium gating current, in part because of the relatively slow rate of channel activation. Working at elevated temperature, a component of gating current has been observed which has the kinetics and steady state properties of the potassium channel, and which we tentatively call the potassium gating current.

Patch clamp measurements have been primarily directed towards determining the amplitudes and durations of currents through single ionic channels. An important conclusion from this work is that, for cholinergic channels, the conductance amplitude is about the same for all agonists. Partial agonists cause smaller macroscopic conductances than do full agonists because partial agonists cause the channels to be open for a smaller fraction of time.

Another experimental generalization is that cholinergic channels tend to have two separate open-state lifetimes. A likely explanation for this is that there are two open states - one corresponding to one bound agonist and the other corresponding to two bound agonists.

Single-channel measurements have also been made on voltage-dependent channels. A complete analysis was made of the characteristics of the calcium-dependent potassium channel in tissue-cultured pituitary cells. The opening rate for this channel was found to depend on both membrane potential and on the concentration of calcium ions at the membrane interior surface.

In order to improve our ability to detect single channels, a method is being developed to extract information about channel durations in the presence of noise and low-pass filtering. This approach consists of two steps. First, the filtering effect is estimated and appropriate corrections made. Then a square wave is extracted from the corrected noisy signal on the basis of Bayesian inference.

The patch clamp has also been used to observe action potentials in developing cells, and hence to monitor changes that occur during development. We found that during the first two weeks of development of embryonic mouse spinal cord cells, there was a rapid increase in spontaneous electrical activity. The time course of this change parallels biochemical changes that had previously been observed.

In addition to the various electrical measurements on channels, several spectroscopic measurements have been made as well. In particular, the binding of agonists to cholinergic receptors was found to cause changes in electron spin resonance of specially prepared spin labels and also causes changes in fluorescence. These spectroscopic changes result from conformational changes of the receptor complex and are antagonized by the same agents that antagonize acetylcholine binding.

A complementary method has been used to study channel structure and function making use of a theoretical analysis of individual channel proteins. Methods were developed to predict three-dimensional protein structures from knowledge

of primary amino acid sequences. These methods (along with other information, such as the structure of drugs that bind to a channel) were used to model specific channels. Work has now been completed on a method to use calculated partition energies of amino acid side chains to determine certain channel structures.

Section on Neural Systems.

The major focus of the Section is an integrated multidisciplinary effort to determine a neural and a biochemical basis for associative learning. The nudibranch mollusc Hermissenda crassicornis has proven to be a most opportune preparation. Hermissenda has made it possible to define a model of associative learning with the same defining features used for vertebrate associative learning. Movement of Hermissenda toward a light source is markedly reduced after repeated pairing of a light stimulus with rotation. This behavioral change is truly associative (i.e., random light and rotation do not produce the effect), persists for at least several days after training and increases with practice. Stimulus specificity for this behavioral change is indicated by the fact that trained animals do not show changes in responsiveness to food or gravitational stimuli. Other features of vertebrate associative learning such as requirement for contingent stimuli and extinction have also been demonstrated for Hermissenda associative learning.

Three sensory pathways essential to the associative learning model, the visual, statocyst, and chemosensory pathways, have been studied. Synaptic relations of identified neurons which mediate this behavior have been described. With knowledge of sensory, interneurons, and motorneurons involved in this neural integration, membrane changes of specific neurons were implicated as primary steps in a causal sequence responsible for the conditioning. Repeated stimulus pairing (but not unpaired or randomized paradigms) results in short-term cumulative membrane depolarization of the Type B photoreceptor resulting in long-term inactivation of an early voltage-dependent outward K^+ current. This causes enhanced depolarizing responses of the Type B cell and, sequentially, increased inhibition of ipsilateral Type A cells, ipsilateral hair cells, interneurons and motorneurons, and ultimately, retarded positive phototaxis. Duing cumulative depolarization produced by repeated pairings of light and rotation, intracellular Ca^{++} is elevated. Elevated intracellular Ca^{++} in turn causes enhanced activity of a Ca^{++}-calmodulin-dependent protein kinase and thereby increased protein phosphorylation. Increased phosphorylation of specific proteins ultimately results in a decreased I_A and the sequence of neurophysiologic and behavioral changes necessary for associative learning.

Intracellular recordings from sensory receptors together with interneurons and central motorneurons have made it possible to define input-output relations of the visual pathway. Intracellular and extracellular recordings have been made in behaving animals. So as to assess individual neuronal activity as it affects behavior, the neural network consisting of peripheral sensory interactions between photoreceptors, hair cells and optic ganglion cells and the visual-statocyst convergence on cerebropleural interneurons (IN) and MN1 cells, was shown to provide a basis for Hermissenda associative conditioning. This system was suggested for conditioning networks in other animals.

Voltage clamp studies of the soma membrane of isolated Type B photoreceptors were shown to have several light-induced conductances (Na^+, Ca^{++} and K^+). In addition, two voltage-dependent outward K^+ conductances, a large, fast, early

current and a slow, late current, were found. The early outward K^+ current, I_A, was found to be greatly reduced in associatively trained, but not control, animals. The kinetics of inactivation of this current were also increased for only the trained animals. This decrease of a specific dark K^+ current with learning was used to explain the increased input resistance of Type B cells (after the somata were isolated from their axons and synaptic endings) from trained animals. A decreased I_A specific to conditioned animals was suggested as the basis for the enhanced Type B voltage response (during and following light steps) which in turn, via known synaptic interactions, can be put forth to account for the learned behavior.

The two voltage-dependent outward potassium currents in the dark, I_A and I_B (a delayed current), have now been described by a quantitative channel model of the Hodgkin-Huxley type. A mathematical model of these conductances together with the light-dependent inward currents sodium channels was used to predict observed responses of the Type B photoreceptor to light stimuli and current injection.

In the Type B cell, under voltage clamp, a single iontophoretic injection of Ca^{++} (0.5 nA, 1 min) was shown to cause prolonged inactivation of I_A but not I_B. Elevation of intracellular Ca^{++} was shown during the steady-state phase of the light response as well as the LLD after light offset by means of differential absorption spectrophotometry after Arsenazo III injection into the cell. These findings suggest that elevation of cytoplasmic Ca^{++} during the LLD is voltage-dependent and thus should also be enhanced when light is paired with rotation during the conditioning procedure.

Prolonged inactivation of I_A was shown to occur when light steps were paired with depolarizing command steps. These results were correlated with changes in intracellular Ca^{++}. All of these results were used to put forth a membrane channel model for acquisition and retention of associative learning.

A series of biochemical studies were performed which suggested that elevated intracellular Ca^{++} together with depolarization cause prolonged I_A inactivation by increasing Ca^{++}-calmodulin protein kinase activity.

Numerous refinements in characterization of associative learning have been achieved during the past year. These include a dramatic extension of the duration of learning retention from days to weeks, the demonstration of contingency and extinction, and the specification of a change in visual discriminatory behavior as the basis for decreased positive phototactic movement following associative training.

The overall program of the Section was productive in several other areas which were supportive of the main thrust of the Section.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01950-11 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Excitable Membrane Characteristics: Voltage Clamp and Impedance Measurements.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. J. Adelman, Jr.	Chief	LB NINCDS
Other:	J. Fohlmeister	Assistant Professor	U. of Minnesota
	C. Tyndale	Electronic Engineer	MBL
	R. Waltz	Mathematician Programmer	MBL
	R. Mueller	Research Assistant	MBL
	J. Sasner, Jr.	Professor	U. of New Hampshire
	J. R. Clay	Staff Fellow	LB NINCDS
	A. Shrier	Assistant Professor	McGill Univ.
	L. Glass	Associate Professor	McGill Univ.
	M. Guevera	Graduate Student	McGill Univ.

COOPERATING UNITS (if any)
Marine Biological Laboratory, Woods Hole, MA 02543; Univ. of Minnesota; Univ. of New Hampshire; McGill Univ.

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Neural Membranes (located at MBL, Woods Hole, MA 02543)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The general aim of this project has been to study excitable membrane characteristics by a variety of physical methods. One aspect has been to improve electrical measurements of excitable membrane characteristics consistent with physical and chemical methods for the study of nerve and muscle membrane ionic channels. Two major approaches are used. The first involves the development of methods for analysis of ionic channel admittances and/or conductances by means of voltage clamp techniques. Programs for carrying out this analysis are developed. Voltage and current clamp experiments are employed to characterize the ionic currents underlying excitability in squid giant axons and chick embryonic heart cells. The contributions of the various currents to voltage oscillations, pacemaker potentials and action potentials are determined by computer simulations based on the voltage clamp measurements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02087-09 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Function and Structure of Ionic Channels: Ion Interactions and Gating Mechanisms.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. J. Adelman, Jr.	Chief	LB NINCDS
Other:	J. R. Clay	Staff Fellow	LB NINCDS
	L. J. DeFelice	IPA Fellow	LB NINCDS
	M. F. Shlesinger	Assistant Professor	Univ. of Maryland
	J. F. Fohlmeister	Assistant Professor	Univ. of Minn.
	J. T. Neary	Biochemist	MBL

COOPERATING UNITS (if any)
Marine Biological Laboratory, Woods Hole, MA 02543; University of Maryland; University of Minnesota

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Neural Membranes (located at MBL, Woods Hole, MA 02543)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.3	3.3	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Voltage clamp experiments are employed to determine functional and structural characteristics of ionic channels in the squid giant axon. Information concerning these characteristics of the ionic channels is gained by studying the interaction of ions which block the passage of normal charge carriers and by studying the effect of voltage upon the opening and closing ("gating") of channels. Computer simulations are performed of discrete openings and closings of single potassium and sodium ionic channels in nerve and heart using results from probability theory and a random number generator. The gating kinetics of stochastic single K-channels are related to the kinetics of conventionally defined conductances. The effects of known potassium conductance blockers on protein phosphorylation in squid axons is studied. Measurements of channel current-voltage relations are made in the presence of channel blockers, such as Rb^{+}, Cs^{+} and Ba^{++}.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02092-09 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Subcellular and Extracellular Structure Associated with Nerve and Muscle.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. J. Adelman, Jr.	Chief	LB NINCDS
Other:	A. Hodge	Senior Scientist	MBL
	R. Mueller	Research Assistant	MBL
	P. Roslansky	Guest Worker	LB NINCDS
	R. V. Rice	Guest Worker	LB NINCDS
	R. Lasek	Professor	Case West. Res.
	R. Waltz	Mathematician Programmer	MBL
	C. Tyndale	Electronic Engineer	MBL
	R. D. Allen	Professor	Dartmouth College
	C. K. Govind	Investigator	MBL
	C. R. Worthington	Professor	Carnegie-Mellon
	J. Metuzals	Professor	U. of Ottawa

COOPERATING UNITS (if any)
Marine Biological Laboratory, Woods Hole, MA 02543; Case Western Reserve; Dartmouth College; Carnegie-Mellon University; University of Ottawa

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Neural Membranes (located at MBL, Woods Hole, MA 02543)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.9	3.7	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to examine the subcellular and extracellular structure of nerve and muscle and relate such structure to function. Electron microscopy in TEM, STEM and analytical electron beam probe modes, such as EELS and EDAX, determination of proteins contributing to these structures and structural modeling are methods used in this study. The following structures are probed: 1) Neuroplasmic lattice, 2) neurofilaments, 3) microtubules, 4) axolemma, 5) glial cell membranes, and 6) myofilaments. Methods developed and used in this study are: 1) Stereoscopic imaging, 2) Optical autocorrelation, 3) fast Fourier transformation (FFT) of STEM video images, and 4) STEM video image filtering and image enhancement using reverse Fourier transformation. Video imaged light microscopy is used to study living neurons in dark field or differential interference contrast.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02273-06 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

An Investigation of Electro-Mechanical Coupling in Excitable Tissues.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. B. Wells	Research Physiologist	LB	NINCDS
Other:	D. E. Goldman	Guest Worker	LB	NINCDS

COOPERATING UNITS (if any)

Marine Biological Laboratory, Woods Hole, MA 02543

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Neural Membranes (located at MBL, Woods Hole, MA 02543)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major portion of the research effort was concerned with mechanoelectric transduction mechanisms in squid giant axons. An input-output relationship was observed and present studies will further define and quantitate this relationship.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02151-08 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Information Processing in Simple Nervous Systems.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI.:	D.L. Alkon	Medical Officer	LB NINCDS
Other:	J. Shoukimas	Staff Fellow	LB NINCDS
	J. Acosta-Urquidi	Visiting Fellow	LB NINCDS
	Y. Goh	Visiting Fellow	LB NINCDS
	A. Kuzirian	Staff Fellow	LB NINCDS
	J. Harrigan	Mariculturist	MBL
	I. Lederhendler	Behaviorist	MBL
	J. Neary	Biochemist	MBL
	S. Leighton	Guest Worker	LB NINCDS
	J. Buchanan	Graduate Student	Northeastern U.
	W. Richards	Graduate Student	Princeton U.
	S. Senft	Graduate Student	Washington U.

COOPERATING UNITS (if any)
Marine Biological Laboratory, Woods Hole, MA 02543; Northeastern University; Princeton University; Washington University, St. Louis, MO.

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Neural Systems (located at MBL, Woods Hole, MA 02543)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
9.0	8.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principle objective is to study the mechanisms by which simple neural networks process information with particular emphasis on mechanisms of learning. The nervous system of Hermissenda crassicornis has proven to be a good model for information processing at several levels: sensory transduction by photoreceptors and hair cells, analysis of synaptic circuitry, changes in synaptic circuitry produced by conditioning paradigms administered to intact animals, as well as to isolated nervous systems, membrane properties modified by conditioning, identification of critical developmental stages for the neural networks of interest, as well as stages critical for learning. Techniques employed thus far to pursue these questions include simultaneous intracellular recording from multiple neural elements, paired stimulation of the visual and vestibular pathways using a rotating table, iontophoresis of fluorescent dyes and electron dense materials, automated behavioral monitoring of intact Hermissenda, voltage clamp of identified neural elements. Other methods include mariculture, subcellular fractionation, protein phosphorylation analysis, and uptake of neurotransmitter precursors.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02088-09 LB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Function and Structure of Membrane Ionic Channels

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Ehrenstein	Research Physicist	LB NINCDS
Other:	L.M. Huang	Staff Fellow	LB NINCDS
	Nava Moran	Visiting Fellow	LB NINCDS
	H. Robert Guy	Research Physicist	LB NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Biophysics, IRP

SECTION

Section on Molecular Biophysics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.3	3.8	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sodium channels that are modified by the addition of batrachotoxin (BTX) differ in many ways from normal sodium channels. For example, the modified channels activate with first-order kinetics and activate more slowly than do normal sodium channels. These results suggest that BTX slows down one of the conformational changes which occur during channel opening, and that this conformational change becomes rate-limiting.

A theory was developed to calculate partition energies of all amino acid side chains as a function of the distance of the α-carbon from a water-protein, a water-lipid, and a protein-lipid interface. This theory was used to develop a program that predicts the manner in which amphipathic α-helices with specific sequences will stack side by side to form a tight protein barrier between water and an apolar lipid phase. The program, in turn, was used to predict molecular conformations for apolipoproteins and for several membrane channel proteins.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02091-09 LB

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mathematical Modeling

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. FitzHugh Research Physicist LB NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Biophysics, IRP

SECTION

Section on Molecular Biophysics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.0	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical modeling for the following phenomenon was continued:

Signal detection and analysis of the square wave currents from single channel opening and closing in a membrane, distorted by noise and low-pass filtering.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02218-07 LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Effect of Drugs on Voltage-Dependent Ionic Conductance in Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.L. Gilbert	Research Physiologist	LB NINCDS
Other:	G. Ehrenstein	Research Physicist	LB NINCDS

COOPERATING UNITS (if any)

R. J. Lipicky, Food and Drug Administration; E. Wenkert, Dept. of Chemistry, Univ. of California at San Diego; H. Pant, National Institute on Alcohol Abuse and Alcoholism

LAB/BRANCH
Laboratory of Biophysics

SECTION
Section on Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.6	2.1	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to better understand how drugs affect the mechanisms of the ionic conductance in membranes which are voltage-dependent and excitable. These studies involve the use of the squid giant axon and the nerve bundles from the garfish. We have continued studies on the mechanism of drug-channel interactions in the squid axon membrane. In particular, we have studied yohimbine and its analogs. In addition, we have studied amiodarone, an antiarrhythmic drug. We have shown that amiodarone has an acute effect on the electrical properties of the squid giant axon. This is one of the very few acute effects observed for amiodarone.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02219-07 LB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Structure and Function of the Perineurium

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.E. Taylor	Research Physiologist	LB NINCDS
Other:	S.I. Rapoport	Medical Officer, Researcher	LN NIA
	N. Shinowara	Staff Fellow	LN NIA
	H. Levitan	IPA	LN NIA

COOPERATING UNITS (if any)
Laboratory of Neurosciences, NIA

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section of Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We demonstrated the multilayer nature of the perineurium and the role of intercellular tight junctions in maintaining structural and functional integrity. Passing AC current across the perineurium demonstrated that its electrical properties could be represented by two resistances and two capacitances. A high capacitance, which could be ascribed to polarization of charge, probably represents the properties of the intercellular tight junctions.

This project has been temporarily discontinued, pending the expected return during Fiscal Year 1983 of Dr. Ananda Weerasuriya.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02316-05 LB

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Comparison of Different Modes of Axonal Stimulation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Ehrenstein	Research Physicist	LB NINCDS
Other:	B. Wong	Staff Fellow	LB NINCDS

COOPERATING UNITS (if any)

G. Ganot, Technion Medical School, Haifa, Israel

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Reversal potentials for two different current components in Myxicola were measured. One component is that induced by mechanical stimulation of the axon and the other component is the leakage current. Both components had reversal potentials of about -45 mV, suggesting that they have a common pathway. Work this year has consisted of writing up and publishing the results of this research. The reference for this publication is:

Ganot, G., Wong, B.S., Binstock, L. and Ehrenstein, G.: Reversal potentials corresponding to mechanical stimulation and leakage current in Myxicola giant axons. Biochim. Biophys. Acta 649: 487-491, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02317-05-LB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Excitable Membranes and Ion Channels in Tissue-cultured Nerve and Muscle Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Lecar	Research Physicist	LB NINCDS
Other:	B. Wong	Postdoctoral Fellow	LB NINCDS
	G. Ubom	Postdoctoral Fellow	LB NINCDS

COOPERATING UNITS (if any)
M. Adler, Laboratory of Preclinical Studies, NIAAA; C.E. Morris, University of Ottawa, Otta, Ontario; Laboratory of Developmental Neurobiology, IRP, NICHD.

LAB/BRANCH
Laboratory of Biophysics

SECTION
Section on Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2.9	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Single-channel currents are measured in isolated areas of excitable-cell membranes using the patch electrode method. Channel gating is studied as a stochastic process in cultured rat muscle, mouse spinal cord neurons, and anterior pituitary cells. Gating kinetics are determined for various synaptic agonists and partial agonists acting on the postsynaptic receptors, for electrically excitable channels and for the calcium-induced potassium channel. Electron spin resonance and fluorescence measurements are done on acetylcholine-receptor protein isolated from electroplax in order to develop a molecular probe for the conformation changes induced by agonists.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02526-01 LB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Gated Ionic Channels in Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. E. Taylor Research Physiologist LB NINCDS

COOPERATING UNITS (if any)

F. Bezanilla, J.M. Fernandez, UCLA Dept. of Physiology

LAB/BRANCH
Laboratory of Biophysics

SECTION
Section on Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	1.0	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Gating currents corresponding to axonal potassium current have been observed.

When dipicrylamine is incorporated into squid axons, large polarization currents can be produced. Comparison of the effect of chloroform on these currents and on "gating currents" leads to the conclusion that the gating process is not sensitive to the properties of the lipids in the axonal membrane.

TAB 9 -- LABORATORY OF CENTRAL NERVOUS SYSTEM STUDIES -- LCNSS/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Central Nervous System Studies

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982

Laboratory of Central Nervous System Studies
National Institute of Neurological and Communicative Disorders and Stroke

The Laboratory of Central Nervous System Studies comprises two major projects: (1) Neurobiology of Population Isolates--the Study of Child Growth and Development, Behavior and Learning, and Disease Patterns in Primitive Cultures; and (2) Chronic Central Nervous System Disease Studies--Slow, Latent and Temperate Virus Infections. Both projects are an outgrowth of the Study of Child Growth and Disease Patterns in Primitive Cultures. It was this parent project that gave rise to the discovery of kuru, a heredofamilial subacute progressive degenerative disease of the central nervous system of the Fore people and their neighbors in the Eastern Highlands of Papua New Guinea, and led to the demonstration that kuru is caused by a serially transmissible virus which possesses unconventional biological and biochemical properties. This was the first demonstration that chronic degenerative disease in man could have virus etiology and directly stimulated the research that led to the discovery of several other slow virus infections of man. The successful transmission of kuru and the isolation of its virus provided the necessary techniques for the subsequent discovery of a viral etiology for some forms of presenile and senile dementias of man, particularly the Creutzfeldt-Jakob type (CJD), and it was this study that has led to the discovery that the agents causing these diseases form a group of transmissible virus-like agents new to the field of microbiology.

These are the only known virus infections without examples of recovery and are unique in their total failure to evoke any immune response to the causative virus. Moreover, familial forms of CJD appear to be the first examples of virus disease of man with genetic (single gene) control of pathogenesis.

During the past year, we have focused much of our attention on high-incidence foci of motor neuron disease with associated parkinsonian syndromes in the western Pacific, specifically, the amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) complexes among the Jakai and Auyu people of West New Guinea, the Chamorro people of Guam, and residents of the Kii Peninsula of Japan. It now appears that these are determined by exposure during infancy and childhood to isolated environmental deficiencies of calcium and magnesium. The resulting hyperparathyroidism causes deposition of calcium and magnesium in soft tissues and brain cells; absorption and metabolism of other metallic cations are also altered. Many years later this causes formation of neurofibrillary tangles and cascading early neuron death resulting in ALS, PD, and mixed neurological syndromes seen in these foci. In all three foci, enormous calcium and magnesium deficiencies of local soil and water have been demonstrated; residents of all three areas obtained all food and water locally. Deposition of calcium, magnesium, and other metals in brain tissue of patients with ALS and PD from Guam and the Kii Peninsula has been confirmed. Now, using electron-probe X-ray microanalysis, we have further demonstration of the presence of enormous deposits of aluminum, iron, magnesium, and calcium. Recent economic changes have brought in imported food and water sources to Guam and the Kii Peninsula where the diseases are disappearing, but this has not

occurred in the West New Guinea focus where the incidence in some villages is over 1000 times that in the United States.

During the past year a great deal of effort has centered on the investigation of the newly-recognized worldwide distribution of hemorrhagic fever with renal syndrome (HFRS). This was the most significant disease among the peacekeeping forces in Korea during 1951-53 and remained largely unexplained during that period. It is now known, largely from the efforts of our group, to occur in much of the Eurasian landmass, carried to man by the respiratory route from wild rodents which are silent reservoir hosts that remain unaffected by the infection. Three strains of this bunyavirus-like virus have been identified: (1) an Asian strain, usually of high virulence, which causes HFRS with up to 20 percent mortality in Korea, the Soviet Far East, Japan, and 19 provinces of the People's Republic of China; (2) a European strain which causes nephropathica epidemica (NE) in Scandinavia and some of the outbreaks of Balkan nephritis in Yugoslavia, Greece, Hungary, and Czechoslovakia; and (3) a strain in wild American rodents in the Frederick, Maryland area identified by presence of antibody in sera and specific antigens in lung tissue (a similar strain not yet known to cause human disease has been found in wild rodents in Virginia, California, and Alaska). Recently, two new forms of this nephropathy have been discovered: (1) a milder form, clinically resembling influenza, occurring in Asian cities from commensal rats; and (2) a more severe form occurring in laboratory workers in contact with infected laboratory rodents in Japan and Relgium. This has greatly widened the interest and concern about HFRS. We have now found the Korean hemorrhagic fever (KHF) form of the virus in urban-dwelling commensal rats in the United States, and antibodies to the virus in native-born Americans. A search is underway to determine whether mild and severe nephropathies caused by these viruses in the United States may have been misdiagnosed, as they have been until recently in Asia.

In the rapidly evolving story of the hemorrhagic fevers with renal syndrome (HFRS), major findings have been made, particularly with regard to the detection of antibody against Hantaan virus in domestic rats and in wild rodents of three genera (Microtus, Clethronomys, and Pleomyscus) captured in the United States. Pursuing this lead, we have recently demonstrated antigen in lung tissues of a high percentage of seropostive voles (Microtus pennsylvaniacus) trapped in Frederick County, Maryland. Cross-immunofluorescent antibody tests suggest that the agent in native meadow voles represents a new member of the HFRS virus group. Efforts are currently underway to propagate this novel agent in cell culture and in laboratory animals and to further characterize its serological relatedness to and antigenic differentiation from the other known viruses of HFRS.

We list the foci of high incidence of disease of great general importance to all of medicine that have been recently located together with the 15 foci reported in our previous annual report; and studies on all of these are underway. These include: (1) focus of high-incidence chronic inflammatory disease of the CNS called Viliuisk encephalomyelitis which appears to be communicable among Iakut people of the Iakut ASSR of Soviet Siberia; (2) high incidence focus of spastic paraplegia (called spastic paraparesis of the Pacific) as seen in half of the Pacific and Colombia; (3) focus of high incidence of ALS and PD in West New Guinea among the Auyu and Jakai peoples resembling similar foci on Guam and the Kii Peninsula in Japan; (4) focus of high incidence of motor neuron disease among Australian aborigines on Groote

Eylandt and adjacent Arnhem Land; (5) focus of high incidence of self-limiting epilepsy as a newly recognized form of cerebral cysticercosis in West New Guinea; (6) focus of high incidence premature aging in certain highland populations in New Guinea; (7) focus of unusually high incidence and early age of appearance of amyloid plaques and neurofibrillary tangles characteristic of neurological aging in certain isolated populations; (8) foci of very much delayed menarche and male and female puberty in isolated Melanesian populations; (9) foci of high incidence spinocerebellar ataxias of diverse types in very isolated highly inbred populations on la Reunion Island in the Indian Ocean; (10) foci of high incidence Huntington's disease in several isolated Amerindian (Venezuelan) and Melanesian (Papua and New Britain) populations; (11) focus of high incidence male pseudohermaphroditism in isolated Melanesian and Australian aborigines; (12) foci of high incidence of presenile dementias of a slow virus etiology in several population isolates; (13) focus of high incidence of familial parkinson's disease in the Agaun Papuan population; (14) foci of extremely high incidence of goitrous cretinism with congenital CNS defects including deafness, mental and motor defects in New Guinea highland populations; (15) focus of congenital Still's disease on Satawal Island, Western Caroline Islands; (16) foci of abnormally high incidence of chronic lung disease, the leading cause of death, and associated with an extraordinarily high incidence of bronchial asthma in childhood on Micronesian islands; and (17) foci of high incidence hyperuricacidemia including juvenile gout on Micronesian islands.

These studies have continued from their roots in the investigation of kuru, which has been detailed in the Monograph published in 1981: "Kuru: Letters and Field Notes from the Collection of D. Carleton Gajdusek", dealing with the first year of kuru investigation. The field journals (32 volumes) and research cinema documents dealing with our work in isolated and primitive populations over the past 25 years are now being used extensively in the studies of child behavior and neuromuscular development, age and speed of puberty, age of menarche, and patterns of aging; different culturally determined patterns of learning, language acquisition, memory, cognition and symbolic representation; differing time, numerical and other quantitative senses and unusual forms of psychosexual development; development and patterns of psychiatric breakdown, juvenile suicide, violence, outbursts of unusual mass hysterias, use of drugs, and other fad-like stereotype behavior patterns in diverse, isolated, primitive social and cultural settings.

Once again other studies of man in isolated and primitive groups as opportunistic investigations of importance to medicine on a worldwide basis were highlighted in the Hitchcock Lectures in January of 1982 at the University of California (DCG), which summarized the results of such research:

MAN IN ISOLATION

1. Infectious Diseases in Isolated Populations
2. Genetic, Toxic, and Deficiency Diseases in High Incidence in Isolated Populations
3. Unique and Unusual Patterning of Behaviour as a Consequence of Isolation
4. Paradoxes of Unconventional Viruses: Host-specified yet viral n-mers, where n is often large
5. Infectious Disease in Primitive Societies

THE NEW GROUP OF MICROORGANISMS CAUSING THE SSVEs

Following the convening of a series of international workshops on the "Subacute Spongiform Virus Encephalopathies and the Structure of the Unconventional Viruses Which Cause Them" held in the latter part of 1978, the staff of LCNSS participated in an international symposium on "Slow Virus" sponsored by NIAID and held at the Rocky Mountain Laboratory, Hamilton, Montana. Eleven papers were presented and have been published (Academic Press); they covered the origin of studies on slow infections in humans, the worldwide epidemiology of these diseases, the pathogenesis and molecular biology of the viruses, the biological, physical and chemical properties of the viruses including the evidence for strain variations and their unusual resistance to gamma and ultraviolet radiation.

The most challenging outcome of the discovery that some chronic progressive non-inflammatory CNS diseases (sporadic, as most cases of Creutzfeldt-Jakob disease (CJD); epidemic, as kuru; or familial, as familial CJD and kuru) are "slow infections" caused by viruses with incubation periods measured in years or decades, has been the realization that the etiologic agents of these infections are new kinds of microorganisms. The absence of antigenicity and their unusual resistance to ultraviolet and ionizing radiation, to formaldehyde and other disinfectants such as β-propiolactone, ethylene oxide, and to heat place them in a group unique among viruses. Their ability to produce fatal CNS disease without eliciting inflammatory responses, the failure of the course of disease or incubation period to be influenced by immunosuppression, and failure to demonstrate any antigenicity in high titer infective virus preparations, or to find any evidence of humoral or delayed hypersensitivity reactions in the diseases, as well as an absence of response to interferon, stimulation of interferon, or interference with interferon production, and absence of interference with known viruses, form the series of atypical biological properties which likewise differentiate these agents from any other group of microorganisms. On the other hand, classical virus properties, such as adaptation to new hosts, broadening of host range and reduction of incubation period, dependence of pathogenic effect on the genetic breed of the host, the presence of strains of differing virulence in wild stock viruses selected by limiting dilution, and the interference of fast-growing by slow-growing strains of scrapie, are all indicative of a complex host-virus genetic interaction characteristic of more classical viruses. Attempts to delineate the chemical nature of the replicating agents, especially to determine whether they are replicated from introduced genetic information or by the induction, derepression or activation of pre-existing genetic information in the host, are the major thrusts of current investigation.

The elucidation of the structure and molecular configuration of the infectious agent of scrapie, CJD, and kuru remains the first goal of this laboratory. For two decades this frustrating problem has been a challenge to molecular biologists, biochemists, and virologists in many laboratories.

In the past year we have made advances in our attempts to characterize the scrapie agent:

A. Cesium chloride fractionation of the infectivity. The general trend of the infectivity distribution in the first sedimentation to equilibrium from homogeneity of the mouse scrapie agent from a mouse brain homogenate has been determined. The infectivity is banding in a broad peak centered around density

1.24. The broadness of the peak indicates a considerable heterogeneity in density. Due to the steepness of the gradient we have achieved a marked separation from other components assayed, i.e., RNA, DNA, protein and lipid. The preliminary infectivity data also indicate that the cesium chloride gradient has concentrated the infectivity relative to a sample stored in cesium chloride and not banded. Purification of 500x with respect to total brain DNA has been achieved.

Individual or combined fractions from these gradients have been assayed analytically for scrapie specific DNA, RNA and proteins by gel electrophoresis but as yet without detecting a new species of macromolecule. The highly complex protein patterns are virtually identical in normal and affected brain except for several protein deficiencies in the affected animal.

Study of the behavior of scrapie infectivity with exposure to high energies of sonication with rise in infectivity titer and fall even on frozen storage thereafter, indicate "sticky" clumping of the infectious units. Theoretical reinterpretation of much of the scrapie inactivation data in the light of the newly proved association or aggregation of infectious units indicates that even the aberrant behavior to UV and ionizing radiation may still be consistent with a larger virus than we previously suspected.

B. Adaptation and development of the hamster 263-K strain of scrapie with high virus yields, shorter doubling time and shorter incubation periods than in mouse scrapie. Scrapie-infected hamster (strain 263-K) is a more suitable source of virus for purification studies. It is associated with a short incubation period and high initial titer of infectivity. The disease can be detected behaviorally only 55 days after a high titer passage, compared with a minimum of 180 days in the mouse system. Several titrations of hamster 263-K brain homogenates have consistently shown initial brain titers of ?-5 x 10^{10} infectious units/gram of brain, over 100 times the titers obtained from mice. In a detailed analysis for biochemical studies and titration purposes, the hamster system is at least two times and, for some purposes, over 500 times more efficient with respect to titration time and required animal space than is the mouse system. In terms of macromolecular distributions the hamster brain has fractionated much the same as the mouse brain. There is also a pronounced dependency of incubation time in the hamster on the dose of the agent, and this feature of the disease can be exploited to give an early indication of the distribution of the agent in fractionations, if not a quantitative assessment of infectivity.

C. The possibility of obtaining infectious nucleic acids from extracted brain tissue. In order to enhance the potential infectivity of any naked nucleic acid recovered by our procedure we coupled the infectious assay with a transfection procedure which we had shown to be effective for herpes simplex virus, ΦX-174. The experimental approach was to fractionate infected mouse brain homogenate following a heat inactivation step (80°C for 30 minutes) designed to inactivate any enzymes that might interfere with the recovery of infectious material. Following heat inactivation the homogenate was digested with Protease K, then extracted with phenol in the presence of 1% sodium dodecyl sulfate (SDS). The resulting three fractions (aqueous, phenol and heavy interphase) were further extracted under conditions designed to preserve the molecular nature of the material finding its way to that fraction. The aqueous phase was further extracted with organic solvents and alcohol precipitated. The

phenol phase was buffer extracted to recover any material and the interphase was buffer extracted to remove the phenol. The resulting fractions were assayed for infectivity in NIH Swiss Webster mice. The results of this experiment clearly indicated that there was no infectivity associated with the nucleic acid fraction. The conditions used in these experiments yielded infectious HSV-1 DNA from infected cells but provided no scrapie infectivity. The heat and Protease K treatment had no effect on the infectious titer, however the subsequent steps destroyed virtually all of the infectivity. The only possible infectivity should have been in the highest concentrations of the buffer extracted interphase from the phenol extraction; the presence of infectivity in this fraction has not been confirmed by pathology. These results suggested to us that the viroid model, at least in its simplest forms, is not valid for the unconventional agents. Further studies on the scrapie system have focused on our impression that an essential, very hydrophobic protein is intimately associated with the scrapie agent and that new procedures are necessary for its isolation.

D. Attempt to detect double-stranded scrapie-specific DNA by molecular hybridization. More recent studies reported in the literature indicate that at least a small percentage of the scrapie population has a DNA component of low molecular weight that is DNAase sensitive which is eluted at 0.48M phosphate buffer from hydroxyapatite columns. This would suggest that the DNA molecule could be double stranded. During this year we tried to detect double-stranded scrapie-specific DNA by molecular hybridization experiments since analysis of the kinetics of DNA reassociation has proven to be a very sensitive means of detecting the presence of specific DNA sequences in mammalian genome. As a probe we used the DNA extracted from concentrated enriched scrapie labeled with I^{125} and annealed to total DNA extracted from infected and uninfected brains of the same and different species. No difference was observed between the extent of reassociation of the probe with DNA of scrapie or normal animals. Our levels of detection indicate that if the scrapie agent were a double-stranded DNA molecule its presence in infected brain tissue is below the level of 50 molecules of DNA per infective unit. We have sought also to repeat the work of others claiming to have isolated a scrapie-specific DNA. However, our attempts to reproduce this much discussed procedure are disappointing with less than a 1% recovery of infectivity in the high speed supernatant as opposed to the 10-90% indicated by Marsh and Malone. When this high speed cell-free virus was placed on a 2.5% polyarylamide-0.5% agar rose gel (9.5x0.6cm tube) at 6 mA of voltage for 2 hours, all of the infectious virus entered the gel and was recovered ($4.8x10^6$). Enzyme treatment of these infectious units was not interpretable due to the total inactivation of the virus at 37°C after 3 hours. These studies are being continued.

E. Comparison of neurotransmitter concentrations in brains of scrapie-affected and normal mice and hamsters in the hope of identifying a particular neuronal system as the target for the infection in the brain. Comparing late scrapie mice with same age controls we have observed normal levels of catecholamines and most amino acids, but a two-fold increase in GABA levels and a nearly 100-fold decrease in 5-hydroxytryptamine (5-HT) levels. This finding prompted us to look at 5-HT levels in the blood. In the case of late hamster scrapie we observe a somewhat variable but significant decrease in blood serotonin of almost two-fold. At present these findings are being vigorously pursued: (1) to discover the time course of these changes and correlate them with behavioral changes and histopathology; (2) to narrow down by behavioral neuropharmacology, and brain microassay of neurotransmitters and

enzymes the specific lesion(s) involved; (3) to identify other non-CNS indicators of these changes which may be of clinical use; and (4) to test the efficacy of 5-HT analogs as a therapy.

Our studies on the therapeutic benefits of the serotonin agonist, quipazine maleate, and the serotonin precursor, L-5-hydroxytryptophan methyl ester, on scrapie infectious hamsters have shown that both drugs effect small but statistically significant improvements on ataxia and action jerks within a rather narrow dose range. At higher doses we observed a dramatic hypersensitivity in the scrapie infected animals to the toxic effects of both drugs. This hypersensitivity syndrome is an intensively studied phenomenon in the rat and has been shown to originate in that system from neuropharmacological destruction of serotonergic nerve terminals. The hypersensitivity that we have observed in the hamster is even more than that which can be induced by neurotoxic agents in the rat. Thus we may support that the scrapie infection in the hamster results in the destruction or degeneration of the axon terminals of the serotonergic nerves. This is the first example of a serotonin hypersensitivity arising as the consequence of a natural disease state.

In our studies of the biochemical levels of serotonin in the brains and blood of scrapie infected hamsters and mice we have observed the following: (1) a highly significant 2.5-fold decrease in the blood serotonin levels in scrapie infected hamsters but no similar change in mice; (2) a highly significant 20% reduction in mouse brain serotonin levels but no similar change in hamsters. This change in mouse brain concentrations is seen only in the late clinical stage of disease; and, (3) a much larger 10-fold decrease in mouse brain serotonin levels after frozen storage for a prolonged period. Our observation of a 2.5-fold decrease in blood serotonin levels in scrapie infected hamsters is the first major change in blood chemistry noted in the subacute spongiform virus encephalopathies.

F. In a continuing effort both to characterize scrapie virus and find ways to inactivate and/or stabilize it we have performed the following inactivation experiments: (1) sensitivity of scrapie to shear forces; (2) sensitivity of scrapie to osmotic shock; (3) sensitivity of scrapie to exhaustive protease treatment; and (4) sensitivity of scrapie to chlorine dioxide. Results of these studies show: (1) overall scrapie infectivity in brain homogenates can be increased at least 17-fold by exhaustive sonication immediately prior to titration. This quantifies to some extent the level of aggregation of scrapie virus in the usual preparations. We have extended these studies to determine whether or not the high intensities of sonic radiation used in these experiments are inactivating infectivity as well as dissociating aggregates as well as investigating the kinetics of reaggregation. (2) Much of the infectivity loss often associated with exposure to high ionic strength buffers is apparently due to enhanced aggregation under these conditions. (3) If scrapie is inactivated at all by powerful proteases this occurs at a much slower rate than for brain homogenate proteins in general. (4) A kinetic analysis of the inactivation of scrapie infectivity by sodium hypochlorite and chlorine dioxide, show both chemicals to be equally effective inactivating 99.9% of the population in the first few minutes of exposure.

A critical analysis of ionizing radiation data and electrophoresis of scrapie has been undertaken during this past year. The conventional wisdom is that the infectious agents of the subacute spongiform virus encephalopathies

(SSVE) are very small, probably even subviral in size. A favorite hypothesis is that they may represent examples of animal viroids. This expectation is based upon the well established resistance of the SSVE to inactivation by ionizing radiation and, more recently, the observation that scrapie infectivity will comigrate with a viroid marker in some electrophoretic gel system. Dr. Rohwer in our laboratory has now offered intriguing alternative interpretations for both of these findings. He has shown that if the SSVE are highly aggregated, as his sonication data indicate (see above), then the traditional first order analysis of the ionizing radiation data is inappropriate. If aggregation is taken into account in the analysis of the inactivation kinetics, the actual size of the scrapie agent must be much larger than that deduced previously from a first order inactivation constant and, in fact, is consistent with the molecular weight of ordinary viruses. He has also shown that, in the electrophoretic systems used to characterize the mobility of the scrapie agent, viruses fractionate on the basis of their charges whereas nucleic acids fractionate on the basis of their molecular weights. In these same systems simple bacteriophages comigrate with much smaller nucleic markers and in fact the two species cannot be used to calibrate one another and separations such as these cannot distinguish viruses and viroids.

FAILURE OF SCRAPIE INFECTION TO INDUCE AN IMMUNE RESPONSE AND LACK OF ANTIGENICITY OF SCRAPIE VIRUS IN HIGH INFECTIVITY TITER

A. During the period covered by this report major efforts have been made to study the interaction of scrapie with the immune system of infected animals. These studies have been done in three parts. First, the search for a new antigenic component on the surface of spleen cells at various times following infection. Second, a systematic examination of the interaction of scrapie with a C3H/HeJ mouse line reported to be unique. Thirdly, the identification and culture of the infectious cell population in the mouse spleen.

The search for a new antigenic component of the surface of spleen cells was based on the possibility that a new cell surface component would not be detected by the humoral immune response but would be detected by the cellular immune system. To examine this possibility, mixed lymphocyte cultures were utilized using two inbred strains of mice, Balb/C and C57BL/6. Two large groups of animals were studied with cultures at weekly intervals over the early and late stages of infection. In every case controls inoculated with normal mouse brain were included on a 1:1 ratio. Data during the early post infection period included spleen weights to check for the enlargement reported by others. Throughout this study the results were uniformly negative with respect to both the splenomegaly and to the presence of any new cell surface component. Several cultural combinations were included to examine the scrapie-infected cells as both target cells and responder cells. It seems clear from this work that: (1) there is no new cell surface component on scrapie-infected spleen cells that can be detected in mixed lymphocyte culture; (2) scrapie-infected spleen cells retain the capacity to respond to the mitogens Con A and LPS as well as respond to a heterologous H-2 determinant in mixed lymphocyte culture. These responses are identical in magnitude to those animals inoculated with normal mouse brain; (3) there is no detectable splenomegaly in scrapie infected mice within the first three months of infection and there is no splenomegaly throughout most infections.

Extensive studies with the C3H/HeJ strain of mouse have not confirmed the published report of other investigators that this strain of mouse, when infected with scrapie, loses its ability to mount a mitogenic response to the endotoxic protein component of E. coli LPS. This animal is genetically unable to respond to the Lipid A moiety. These studies were carried out at weekly intervals from weeks 2 through 7, since previous reports indicated the peak depression to occur at week 4. It has been reported that a marked spleen enlargement occurred, a finding also not confirmed in this work. There are only two possible explanations for the lack of agreement--one is a difference between the Chandler and C506 strains of scrapie, or that other investigators had a contaminating virus in their inocula. The plan for the future is to attempt to determine which of these is the explanation and to attempt to clarify completely if there is or is not a measurable change in the immune response of C3H/HeJ mice with scrapie.

The results of the spleen cell sub-population studies have been completed. It is clear that strain C506 gives extremely low spleen titers and that only as very small number (less than 1 in 10^5) spleen cells are infectious, whatever sub-population they are in. Extensive studies on splenic macrophages in culture have been disappointing from the point of view of continued infectivity.

We have also explored the ability of scrapie to grow in vitro in well-established, 'T', 'B' and macrophage cell lines of murine origin. Two questions are being investigated: (1) does the cell have a receptor for scrapie on its cell surface?; and (2) if it does not have a receptor (assuming that scrapie agent is the free nucleic acid bound to lipid membranes), do other methods have to be used to get the agent in the cell so that it could replicate? Inactivated Sendai virus and lysolecithin were used as membrane-fusing agents; DEAE-Dextran, which alters the permeability of the membrane and is used for assay infectivity of other viral nucleic acids in cell culture, was also used. Cell culture harvests from these experiments have been titrated in mice for infectivity and the results from these experiments will help us answer the two questions. Since most of the murine cell lines used in the study have endogenous C-type viruses, it will also be interesting to see if these viruses act as helper viruses for the growth of scrapie. Attempts to grow scrapie in mosquito cells: Aedes albopictus mosquito-cell lines have been used to grow several groups of arboviruses. In such cells these viruses grow at 22°C without producing cytopathic effect, and infected cells become chronically infected by the virus. Virus is released from these chronically infected cells into the medium. We have inoculated these cells with the scrapie agent, and cell lysates at different passage levels have been inoculated into mice for the assay of infectivity. Results were discouraging since unlike some members of the togaviruses, scrapie infectivity was not recovered from inoculated insect cell lines. An SV-40 transformed cell line that contained scrapie virus at the 12th passage level was serially passaged to higher levels; none of 50 pooled and cloned cultures was infectious for mice at the 30th passage level or higher. The scrapie-infected SMB line of Clarke and Haig was imported from England; five lots of this line have been prepared and aliquots stored; mutants of the cells are being prepared. A line of cells was derived from the brain of a hamster infected with the 263-K strain of scrapie; this line is also under study.

B. Since conventional immunological techniques have thus far failed to elicit an antigen-antibody reaction in kuru, Creutzfeldt-Jakob disease or scrapie, we have been attempting to produce specific antibody to scrapie by the

hybridoma technique of Kohler and Milstein since it has been shown that cells from a mouse myeloma could be fused with splenic cells from mice stimulated with an antigen, and such fused cell clones produce specific antibody which is monoclonal for individual antigenic determinants. Such a technique facilitates antigenic analysis of complex antigens. In our studies spleen cells from mice immunized with scrapie infected mouse or hamster brain scrapie specific antibody has not yet been obtained; however, 30 monoclonal antibodies were derived which are reactive to antigens in hamster or mouse nervous system tissues. Of the 30 clones analyzed, specificity included clones reacting with grey matter of mouse and hamster brain, one clone reacting with axons in animal brain, several clones reacting with cytoskeletal proteins (intermediate and micro-filaments) and 19 clones which produced antibody reactions with both neural and non-neural tissue components.

C. We also measured the general immunocompetence of splenic lymphocytes in an attempt to detect alterations of the immune system of scrapie affected animals. In general splenic activation by Concanavalin A, phytohemagglutinin and lipopolysaccharide of control and scrapie inoculated mice were compared. Mitogen-induced responses of splenocytes from infected and control cultures were not significantly different. The PHA response of scrapie-infected mouse spleen cells was slightly depressed over a period of 29 to 56 days post-inoculation. Additional efforts to induce scrapie specific antibody are underway and indeed the use of several different preparations of high-titering scrapie infected hamster brain that has been subjected to (a) chemical tissue membrane modifers, (b) purified by density gradient banding, and (c) tied up with haptens. Such mitogens are being assayed in animals rendered immunotolerant to uninfected hamster brain.

As a control for the scrapie studies, somatic cell hybridization to produce monoclonal antibody against a major glycoprotein (P_0 30,000 MW) associated with human peripheral nervous system myelin was carried out. Thus far we have produced two clones both of which react with peripheral nerve myelin; only one produces antibody specifically reactive with the P_0 low molecular weight glycoprotein.

D. Since the demonstration of cell-fusing activity in the majority of brain extracts of scrapie mice and CJD patients (see ANNUAL REPORT: October 1, 1977 through September 30, 1978), additional studies have been carried out using two different techniques. One involved the formation of multinucleated cells and the other the formation of somatic hybrid cells. Heterokaryons were measured at 18 hours and hybrid cells after an average of 25 days. The studies employed three scrapie cases, 32 cases of transmitted CJD, two cases of untransmitted CJD, 26 cases of other neurological diseases, three transmitted cases of other than CJD and 17 patients without neurological disease. The results show a significantly higher proportion of CJD brains (61%) was positive than other neurological diseases (31.4%) or the control group (6%). Thus our earlier observations have been clearly confirmed and although the assay does not separate CJD from other neurological diseases to warrant its use as a specific diagnostic test we hope that such discrimination can be improved to the extent that the detection of cell-fusing activity might be possible utilizing serum, urine and CSF from patients and their family members as a biological marker of this disease. We shall continue to study the phenomena of cell fusing activity in an effort to elucidate the mechanism in CJD and other neurologic diseases as well as the application of this technique as a rapid means of more quickly

measuring infectivity in experimentally derived fractions from purification procedures employed for scrapie and CJD.

Recently study of the appearance of this cell fusing activity in brain of hamsters infected with scrapie has shown peak fusing activity attained early in incubation (4 weeks) instead of during clinical disease (8 to 9 weeks). This may indicate the desirability of studying hamster brain early in the incubation period for possible biochemical markers of scrapie virus or scrapie activity.

E. Resistance to high concentration of formaldehyde, to heat up to 85°C, and to ultraviolet radiation at 254 nm, and an ultraviolet sensitivity at 237 nm greater than at 254 nm have been found for kuru and CJD viruses as for scrapie. These very unusual physical properties greatly emphasize our current contention that the viruses of the human diseases are closely related to the scrapie virus. great relevance to the etiology of the plaque of Alzheimer's disease. Similarly, the two human agents have been shown to have the same enormous resistence to ionizing radiation (gamma rays from Cobalt CO_{60} as is found for scrapie virus. The most direct inference from this enormous resistance is an effective size of under 100,000 daltons molecular weight. Although many possible explanations, including atypical fine structure for a nucleotide configuration and unusually efficient nucleic acid repair mechanisms have been suggested to account for such anamolous properters, the simplest explanations namely, that in fact the agents are of such small size, may be true; or, the new data of extensive "sticky" clumping or aggregation of infectious units may account for much of the anomalous behavior.

REVISION OF SURGERY AND AUTOPSY ROOM TECHNIQUES FOR DEALING WITH DEMENTIA PATIENTS

A. Precautions for handling CJD patients in hospitals and in operating and autopsy rooms and laboratories. The discovery that the worldwide-distributed Creutzfeldt-Jakob disease is caused by a serially transmissible, self-replicating agent that passes through bacteria-, protozoan- and fungus-retaining membrane filters, the demonstration that the virus is widely distributed in non-CNS tissues and fluids of affected patients and possesses great resistance to usual antiseptics, has also resulted in a growing concern among medical and paramedical nursing and laboratory personnel, particularly neurologist, neurosurgeons, pathologists, and anesthesiologists, about the potential hazards involved in caring for patients with presenile dementias and handling their tissues. Concern comes largely from recent reports documenting transmission of Creutzfeldt-Jakob disease by corneal transplant, the accidental inoculation of two patients in neurosugery with CJD-contaminated electrodes used in stereotactic electroencephalographic recording and stimulation, the suspicion that a neurosurgeon and two general practitioners may have contracted CJD from patients and the characteristic greatly over-represented among patients with CJD of a history of brain or eye surgery in the previous two years before onset of clinical disease. These concerns have further been hightened by the recent transmission of CJD to a chimpanzee by implantation of the same silver electrodes that caused disease in the two human patients after more than two years storage in formaldehyde vapors ued for sterilization. In response to these concerns we have published precautions for conducting biopsies and autopsies and have more recently, presented a summary on the current knowledge of the pathogenicity and communicability of CJD and related subacute spongiform

encephalopathies of man and animals which are caused by similar unconventional viruses. We have also made recommendations on the rational precautions that should be taken in caring for these patients and in handling their tissues and helped establish guidelines for safe handling of the SSVE viruses in laboratories.

B. Studies on the inactiviation of the SSVE viruses. During the last year, inactivation studies were made with disinfectants using mouse scrapie agent. Mouse scrapie, kuru and CJD agents seem to have similar properties. Disinfectants used were clorox, organic iodine (Wescodyne), potassium permanganate, hydrogen peroxide, and Zepharin. Since ethylene oxide gas is commonly used in hospitals, ethylene oxide was also used. The data showed that after chlorox, a 1:250 dilution of $KMNO_4$ was the most effective disinfectant, followed by Wescodyne and ethylene oxide, which reduced infectivity by 99 percent. Under the experimental conditions used in the study hydrogen peroxide did not affect the titer of the scrapie agent at concentrations used in the hospital environment. Residual toxicity of Zepharin for mice was high. Further studies are in progress on the CJD agent, with ethylene oxide autoclaving used for sterilization in the hospital setting. Finally, chloride dioxide has been examined in parallel with potassium permangenate for inactivation activity against a guinea pig-adapted strain of CJD virus; and chlorine dioxide, sodium hypochlorite, potassium permangenate, hydrogen peroxide, and lysol® have been tested for activity against a hamster-adapted strain of scrapie. Time-dose experiments are on titration at this time, and should be completed within the year. Depending upon the results further recommendation will be made to the medical community. However, it is already apparent that some scrapie virus infectivity remains in hamster brain tissue of high titer after autoclaving and after eythlene oxide sterilization and that chlorox remains the most effective disinfectant.

NATURAL HISTORY OF TRANSMISSIBLE VIRUS DEMENTIA
The Search for the Source of Infection in Man

In an effort to determine the method of spread of CJD virus in man, we have recently completed a comprehensive worldwide epidemiologic survey of CJD. It is shown that in the United States the average annual mortality is at least 0.26 deaths per million population. Temporal-spatial clustering of cases was found in the United States, but reports from other countries indicate that this occurs. Fifteen percent of the cases were of the familial type, suggesting a genetic susceptibility to infection. In this survey, some evidence was found that previous surgery of pre-existing neurologic disease may be associated with an increased risk of developing CJD.

A systematic investigation of all cases of CJD dying in France during the decade 1968-1977 was completed last year and updated through 1980 this year in collaboration with Dr. Francoise Cathala and members of the French Neurological Society, with a view towards clinical definition of a large and unselected case series, and to obtain some clue as to the natural mode of disease transmission. One hundred and seventy cases were discovered, of which 124, confirmed by autopsy or biopsy,were the subject of multifactor statistical analysis. The disease forms a clinical spectrum from nearly acute encephalitic type illness with a few weeks' rapid progression and death, to lingering illness of years' duration, impossible to diagnose in the absence of neuropathological verification. Types of clinical onsets, range of symptoms during the course

of illness, and symptom combinations with the highest frequencies were analyzed in detail. In addition, epidemiological data on all 170 cases were examined for the possibility of iatrogenic or case-contact types of human-to-human transmssion. Apart from the approximately 10% of familial cases, no contact could be established between any two patients in France during a 10-year period, medical profession, and those cases in paramedical professions did not occur at a higher rate than in the general population. Close examination of familial cases established that even in such families, personal contact between two subsequently affected members does not always occur, suggesing ever more strongly the participation of predominantly genetic factors in the familial type of CJD. Our epidemiologcal studies have already indicated that an annual incidence of nearly one case per million can be expected when newly occuring cases are actively searched out. The frequency of the disease continued to be highest in the densely populated center of Paris, raising further speculation about human-to-human modes of natural transmission. On the other hand, study of exceptionally isolated cases, which could simplify examination of the number of possible routes of acquiring the disease, still has not yielded any clues to this problem. A full-scale study of any possible association of CJD and scrapie in sheep is also under way.

A detailed analysis of the clinical features of the first 100 transmissible cases of CJD has been performed, and the results compared to the clinical features of a similar number of cases of Alzheimer's disease. There is a considerable overlap in the clinical spectrum of both diseases, and a group of patients with Alzheimer's disease with myoclonus has been delineated for further clinical and pathological evaluation. In addition, the clinical syndrome of "amyotrophic" CJD and a group of cases of "untransmissible" CJD are being studied.

Other clinical features of CJD which may be related to different strains of the virus are bein examined. A manuscript is in preparation describing a small number of cases of CJD with the clinical features of progressive supranuclear palsy. The differences between the acute and chronic forms of CJD have already led to the discovery of a virus strain from a Japanese case that takes readily in non-primates and causes both gray and white matter spongiform lesions. The possibility that the virus also causes previously unrecognized childhood encephalopathies is also being investigated.

In a continuing investigation on the possible modes of natural transmission of the CJD virus, we are intensively evaluating the familial occurrence of the disease. To date, we have identified 37 families with a total of 155 affected members. CJD occurs in a pattern suggesting autosomal dominant transmission. Compared with the sporadic form of CJD, in familal CJD the age at death is slightly earlier and there is a female preponderence. The clinical and pathological features are otherwise indistinguishable. No maternal effect was found. There was some evidence for anticipation. An analysis of temporal and spatial separations between affected family members suggest that if contact transmssion were occurring, incubation periods up to four decades might be expected. However, the available data do not yet allow us to distinguish between a genetic susceptibility to infection or some form of vertical transmission. Studies are in progress determing genetic markers, such as the HLA type, of both sporadic an familial CJD, which might give us an indication of the genetic component of susceptibility to infection.

NEUROPATHOLOGICAL SURVEILLANCE OF CJD AND KURU

A major part of our experimental studies on CJD include the routine screening of the brains of all animals dying after inoculation with various chronic neurologic diseases, since it is now known that in the case of the squirrel monkey at least, approximately 15% of the animals die without showing clinical signs of neurological disease. The topography of the spongiform change has recently been analyzed in more than 200 squirrel monkey brains, where the results indicate that considerable variation in the severity and distribution of the lesions occur. The differences between CJD, kuru and scrapie are being examined in both primate and non-primate hosts. The unusual white matter change produced by a Japanese strain of CJD in mice is being examined.

A re-evaluation of the spongiform change in human kuru is being performed to see if the same general features as seen in human CJD also occur. The peculiar amyloid plaques that occur in 60% of kuru patients and approximately 10% of CJD patients is being investigated both structurally and at a biochemical level. The occurrence of these amyloid plaques in a virus-induced encephalopathy has

SCRAPIE AND CJD VIRUS ALTERATIONS IN INTER-SPECIES PASSAGE

With our demonstration of the transmissibility of scrapie disease from American sheep and English goats to several species of non-human primates, manifested by a disease in the experimental monkey that is indistinguishable from the transmissible virus dementia originating from man, we are confronted with the urgent question of the possible relationship between scrapie of sheep and the spongiform encephalopathies of man. The scrapie virus is capable of infecting all species of monkeys tested. However, the Compton (English goat) strain after passage through non-human primates no longer induces disease when inoculated back into sheep or goats. Of tremendous importance has been the discovery that although these same strains of non-human primate-adapted scrapie virus did not induce clinical disease in mice during the more than two years they were observed, such mice did in fact have neuropathological lesions of spongiform encephalopathy in their brains and sub-inoculation of this material did induce disease in other mice. A similar observation has now been made on CJD in mice wherein transmission occurred on primary passage of human brain but on the first mouse to mouse passage animals remained asymptomatic for over 2-1/2 years yet when killed histopathological evidence of spongiform encephalopathy was observed in their brains. Thus, we have evidence that infected animals can remain asymptomatic and that in these animals the incubation period before onset of clinical disease may exceed the life span of the host.

The same exceptionally long incubation periods are evidenced in those few cases of kuru that have occurred in the Fore of Papua New Guinea during the past five or six years; new cases occur only in patients over 20 years of age.

PATHOGENESIS OF CJD IN MICE

The biological properties of scrapie appear to be altered after passage through the primate host--behavior, not unlike classical viruses; such altered biological properties may account for the failure of CJD and kuru viruses to induce disease in mice routinely. We have experienced difficulty in adapting

the virus of CJD to mice and guinea pigs, but in recent experiments some passage lines of CJD have caused spongiform encephalopathy in both guinea pigs and mice, and we have recently completed studies on the pathogenesis of the Japanese strain of the virus in Balb-C mice. The findings were strikingly similar to the pathogenesis of scrapie in the mouse with a few notable exceptions. Initially, characteristic spongiform degeneration of the brain was first noted pre-clinically at 9 weeks following inoculation. Clinical signs did not become apparent until 16 weeks with the geometric mean incubation period being 112 days. Infectivity assays of various tissues of inoculated mice resulted in recovery of virus from brain and spleen as early as one week after inoculation. Furthermore, the average incubation period of mice inoculated with spleen was markedly less than that of mice injected with brain material from the second through the sixteenth weeks of incubation indicating that the concentration of virus is higher in the spleen than in the brain during the asymptomatic period. Lesser amounts of virus were detected in thymus, lung, and kidney. In the kidney the virus appeared late in the pre-clinical period and the incubation period for recipient mice were prolonged. Virus was not detected in the liver in contrast to its presence in this tissue in human patients. Viruria was not demonstrable. However, we did confirm the presence of a viremia in CJD infected animals beginning during the sixth week after inoculation. Concentrations of virus in the blood at the 14th and 18th weeks were estimated to be appreciable since the incubation periods in recipient mice ranged from 4 to 5 months. The clnical disease was confirmed histologically.

ORAL TRANSMISSION OF KURU AND CJD

We have now proven the transmissibility of the spongiform viruses by the oral route through feeding of virus-infected whole tissues. Two of two squirrel monkeys fed CJD-infected chimpanzee tissues and two of two squirrel monkeys fed scrapie infected whole tissues developed clinical disease and had typical pathological lesions of the spongiform enceohalopathy in their brains. One of two monkeys fed kuru-infected chimpanzee tissues developed spongiform encephalopathy. The asymptomatic incubation period in the one monkey exposed to kuru was 36 months; those in the two monkeys exposed to CJD virus were 23 and 27 months, respectively; and those in the two monkeys exposed to scrapie virus were 25 and 32 months, respectively. The one additional animal similarly exposed to kuru has remained asymptomatic during the 45 months it has been under observation.

ANTI-NEUROFILAMENT ANTIBODY

The discovery of an heterogeneic autoantibody in the sera of kuru and Creutzfeldt-Jakob disease patients to neurofilament protein (Sotelo, Gibbs, and Gajdusek, SCIENCE 210:4466(October 10), 190-193, 1980) using mature neurons of murine origin in culture as antigens (Sotelo, Gibbs, Gajdusek, Toh, and Wurth, PNAS USA 77: 653-657, 1980), has initiated a series of in-depth studies to characterize the autoantibody and to determine whether or not it in any way shows specificity to the viruses causing the subacute spongiform encephalopathies. To date this does not on the surface appear to be the case since this autoantibody has been found in lower frequency in the sera of patients with other human neurological diseases. However, the possibility that our "unconventional viruses" utilize a host cytoskeletal protein in their structure as do some other viruses demands that this "non-specificity" be not too glibly dismissed. Already it is evident that its presence is not diagnostic

of the subacute spongiform virus encephalopathies and its presence in high titer in the sera of Guamanian patients with amyotrophic lateral sclerosis and parkinsonism-dementia, patients with Alzheimer's disease, and other neurological diseases warrants this conclusion. However, the detection of this heterogenic autoantibody has led to the particularly intriguing observation that it is remarkably specific for a small filament only in the axon of the cell unlike that of experimentally prepared antisera to neurofilament protein which reacts with filaments in both the axon and the dendritic processes of neurons. Finally, although unencumbered neurons of murine embryos in our in vitro test provide the best method for the detection and study of this immune reaction, its detection in mass screening has been much facilitated by the use of the indirect fluorescent staining of frozen and fixed sections of rat embryo spinal cords (Bahmanyar et al., NEUROLOGY 1981). Already to our surprise the antibody has not been found in a large series of sera from patients with autoimmune collagenous diseases which were positive for anti-rheumatoid factor and anti-DNA antibody. The possibility that these unconventional viruses use a filamentous cytoskeletal protein of the host in their structure as do some bacteriophages and plant viruses must be considered.

NEWLY EXTENDED RANGE OF CLINICAL DISEASE ASSOCIATED WITH CREUTZFELDT-JAKOB DISEASE DIAGNOSIS

In a paper in press in BRAIN (Masters, Gajdusek and Gibbs) we are presenting data of the transmission of spongiform encephalopathy to non-human primates inoculated with three atypical cases of CJD. They were atypical because of the presence of an unusually long course, the early clinical appearance of ataxia and other cerebellar symptoms, the very slow and only moderate degree of dementia, and neuropathologically revealing extensive distribution of amyloid plaques resembling those observed in kuru patients. These cases show a remarkable similarity both clinically and pathologically to New Guinean kuru, much more so than does the more classical CJD patients we have studied. In an extensive review of the world literature we have found a large literature reporting this type of disease not usually diagnosed as CJD and often occurring in heredofamilial clusters. In such families many of the affected members have little or minimal dementia. Thus, the strong possibility that we must now search for the CJD virus in a wider group of patients than those with the presenile dementia of classical CJD has been demonstrated. Specifically, patients with spinocerebellar degeneration are called to question. In our report in press we are calling the cases comprising this syndrome, not previously brought together, the Gerstmann-Straussler syndrome.

LONG-TERM INCUBATION PERIODS OF KURU, CREUTZFELDT-JAKOB DISEASE AND SCRAPIE IN NON-HUMAN PRIMATES

The year-to-year surveillance of the occurrence of kuru in Papua New Guinea by direct clinical observation has shown that the incubation period in the human population at risk can be as long as 20 to 30 years following exposure. A recent analysis of our laboratory transmission data from non-human primates maintained longer than thought reasonable by investigators in the field of infectious diseases clearly supports the clinical observation made in New Guinea. Nine non-human primates developed experimental kuru following incubation periods which have ranged from 6 to more than 12 years. Of

particular importance among this group were two chimpanzees that had been injected by peripheral routes only (iv,ip,sc,im) and a spider monkey which had been injected intracerebrally and intravenously with a pool of visceral tissues (liver, kidney, spleen) and developed disease 142 months, 82 months, and 123 months, respectively, following inoculation. Similar long incubation periods have been observed in animals inoculated with CJD infected tissues (72 months- 117 months) and scrapie infected tissues (72-74 months). In addition to the intracerebral route we have now conclusively demonstrated that these diseases can be transmitted by the following individual routes of inoculation: intravenous, intraperitoneal, subcutaneous, intramuscular, interdermal, intranasal, and oral. The later findings coupled with the extremely long incubation periods, particularly noted following peripheral inoculations since this is the most likely route of natural infections, have great impact on our epidemiological studies and research into the etiology of other degenerative neurological diseases.

SUMMARY

The elucidation of the etiology and epidemiology of a rare, exotic disease restricted to a small population isolate--kuru in New Guinea--has now brought us to worldwide considerations that have importance for all of medicine and microbiology. For neurology, specifically, we have considerable new insights into the whole range of presenile dementias, and, in particular, to the larger problems of Alzheimer's disease, familial and senile dementias, and the processes of CNS aging. The implications of vertical transmission of slow virus infections, of conjugal transmission of these diseases, and of host genetic control of disease expression for all genetic diseases, and the relationship of these slow virus infection processes to those which may lead to neoplastic transformation are obvious.

The major problem among the degenerative diseases of multiple sclerosis, Alzheimer's diseae, amyotrophic lateral sclerosis, and Parkinsonism remain unsolved, although there are tantalizing laboratory and epidemiological data pointing to the possible role of virus-like agents in these diseases. Perhaps the masked and defective slow infections with conventional viruses such as are seen in PML and SSPE may provide the best leads for studying these diseases.

AMYOTROPHIC LATERAL SCLEROSIS AND PARKINSONISM DEMENTIA IN HIGH INCIDENCE FOCI

Our scientific direction of the amyotrophic lateral sclerosis (ALS) studies at the Guam laboratory of NINCDS for the study of the ALS-PD complex in high incidence among the Chamorro people, has resulted in some 12 publications which have already appeared, or are in press, and many promising ongoing studies. These are summarized below, but they indicate our conviction that the answer to the perplexing problem of motor neuron disease (ALS) and Parkinsonism-dementia (PD) are to be found in these ethnically and geographically limited foci.

Our study of the similarly intense focus of ALS and Parkinsonism and dementia among the isolated Jakai and Auyu people of Western New Guinea, discovered during our field studies (New England Journal of Medicine, 1963), and with two recently updated reports just published (Ciba Symposium, 1977; Symposium on ALS, February ?-3, Tokyo, 1978) (Neurology, in press) is proceeding with further field work this year. This year's work has proven that the disease is fully environmental and that ALS and PD are related as evidenced by (1)

husband and wife with classical ALS; (2) husband with pure PD, wife with classical ALS, simultaneously; (3) next door neighbor to (2) above with classical PD; and (4) two women with classical ALS in 1974 in same village and a neighbor with PD. It appears that the "rule" is that people living or drinking exclusively from small springs and rivers originating in the "red-soil" lowland plain get ALS/PD. People of the same cultural and linguistic groups as these suffering from ALS and PD but living on tidal flats and on big rivers originating from the high mountains do not get ALS/PD. The water and soil analyses indicate extremely low calcium in garden soils and drinking water and the pattern of occurrences seem, as in endemic goiters to follow geological features of the environment rather than the patterns of ethnic and cultural demographic distribution. With this in mind, we are covering possibilities of mineral metabolism, imbalances and trace metal toxicity as well as those of an endogenous virus in an isolated population in our studies on Guam and West New Guinea.

We have increased our collaborative research with the Japanese investigators, who have been helping us on Guam by providing us each year with a young neurologist to assist in the clinical neurological surveillance and care of our patients there and in collaborative pathological, biochemical and pharmacological studies. During this reporting period, Dr. Takao Makifuchi, of the Brain Research Institute, Niigata City, Japan, took up residence on Guam as a Visiting Scientist; and now Dr. Kiyomitsu Oyanagi has arrived to replace him. Also, Dr. Richard Yanagihara was recruited for Guam, and after three months of intensive preparation and developing protocols here at NIH proceeded to Guam where he initiated a study of calcium, phosphorus, magnesium, and trace metal metabolism including Ca47 calcium trace studies on ALS, PD and control subjects.

The Japanese are themselves concerned with their own foci of high incidence of ALS and PD on the Kii Peninsula of the main island of Japan. The series of meetings and conferences on ALS in Japan held in March 1978 resulted in the confirmation by Dr. Hirano of the pathological identity of the Kii Peninsula PD cases with those on Guam (both demonstrating neurofibrillary tangles), and the final agreement that the two disease foci represent the same disease complex. During his 1979 field studies in West New Guinea, the Chief, LCNSS, has obtained definitive evidence that classical Guamanian ALS, PD, and ALS/PD does occur in the high incidence foci he discovered in West Irian and is very excited about resolving this problem. In addition, Dr. Gajdusek noted the occurrence in West New Guinea of a subacute progressive paralysis that looks like "slow-poliomyelitis" vitamin B deficiency. He has seen many cases this year and recognized it as the same disease he first saw in 1974-1976 field trips. The disease is not ALS; it can be "acute", it is often fatal, but remissions and recurrences do occur. A few cases have had beriberi-like edema with onset but most have not. That this very severe paralytic disease should occur within the ALS/PD focus is amazing. International collaboration and, most importantly, more original and innovative research concepts and more imaginative and cautious study of the various Western Pacific foci have continued and been expanded. Those studies which are underway in our collaborative project, and a bibliography of recent publications (1975-1980 in press) resulting from studies of these foci are included as an appendix to this annual report. The ongoing studies include:

(1) Clinical variations in ALS-PD complex in Chamorros;
(2) Human biology of ALS-PD complex and other chronic diseases in Chamorros of the Mariana Islands;
(3) Chronic CNS disease and disability survey of Guamanian Chamorro migrants to the mainland United States;
(4) Genetic studies of the Chamorro population, both normal and ALS-PD afflicted;
(5) Detection of sedimentable reverse transcriptase activity in the brains of patients dying with ALS-PD;
(6) Search for biochemical defects in ALS-PD brains by gel diffusion chromatography;
(7) Search for nucleic acid repair mechanism defects in transformed leucocyte cell lines derived from ALS-PD patients;
(8) Search for an ALS or PD specific antigen in brain tissues by clonal myeloma cell hybridization with spleen cells of ALS and PD from hyperimmunized animals and resultant monoclonal antibody production;
(9) Trace aluminum and other heavy metal studies in brain, CSF, blood and other tissues of ALS-PD patients;
(10) Evaluation of the precise nature of the cognitive and affective defects and the progression of dementia in the PD patient;
(11) Evaluation of liver function and pathology;
(12) Development of techniques for the unmasking of an infectious agent by in vitro techniques;
(13) Assessment of the immunological competence of patients;
(14) Attempts to transmit ALS-PD to non-human primates and non-primate hosts;
(15) Major virus group seroepidemiology of the Mariana and Caroline Islands, Japan, and West New Guinea populations with relation to ALS-PD;
(16) Pharmacologic studies of ALS-PD;
(17) Elucidation of osteoporosis, osteoarthritis, and bone deformities in the Chamorros; and
(18) Evaluation of the growth and development of normal Guamanian children and adolescents--a 30-year follow-up study.

The genetic studies, already well advanced, include blood group factors, red cell enzymes, serum proteins, HLA typing, and mixed leucocyte agglutinins, dermatoglyphics, anthropometry and other gene markers.

Epidemiology of ALS and PD in Migrants to and Immigrants from Guam

Since World War II, there has been an extensive migration from Guam of at least 15,000 Chamorros, primarily to the United States. This represents nearly one-third of the total Chamorro population of 47,000 residing on Guam. Amyotrophic lateral sclerosis has developed in 14 Chamorro migrants from Guam to the United States, Japan and Korea after periods of one to 36 years of absence from Guam. Nine of these cases have been previously reported. In another eight subjects ALS has developed within 1 to 14 years of their return to Guam after absences of many years from the islands. Parkinsonism dementia, a high incidence presenile dementia peculiar to Chamorro Guamanians, has developed in one subject 46 years after his departure from Guam. It appears that the onset of ALS in these patients after long absences from Guam will demonstrate the lower limit for the incubation period in each case if a toxic or infectious exposure occurring only on Guam is the cause of the disease.

Additionally, during the past two decades there has been an increasing number of cases of Guamanian ALS in long-term Filipino migrants to Guam. The average annual incidence rate of ALS in these migrants is approximately five-fold higher than the rate of ALS in the United States. Parkinsonism dementia-like disease has been clinically identified in five Filipino patients and one case with autopsy verified pathologically. Because of the high degree of genetic similarity between the Chamorro and Filipino peoples, which we have recently demonstrated, a detailed epidemiological survey for ALS and a clinical search for PD in the Philippine Islands is currently being conducted by members of this laboratory.

The clinical and pathological characteristics of long surviving cases of Guamanian ALS, that is of more than ten years duration, are currently under study. Long surviving cases of ALS in Guam are younger, have a familial occurrence, have a different sex ratio, and show a different pattern of disease progression than those with a normal duration of disease.

Immunology of ALS and PD on Guam

Additional studies on HLA, dermatoglyphics and other gene markers, on osteoporosis and osteoarthritis, on heavy metals and other environmental toxins and on a ten-year follow-up study of the descriptive epidemiology of ALS and PD are close to completion. Further studies based on these data are in the planning stages or already underway.

Previous studies in our laboratory have shown that ALS and PD patients from Guam had diminished levels of cellular immunity as determined by diminished response to skin test antigens, lymphopenia, diminished number of 'T' cells, and decreased mitogenic response, than those of age- and sex-matched Guamanian controls. Further, ALS patients with HLA BW-35 had diminished cellular immunity and shorter mean duration of the disease. This association was found to a lesser degree among PD patients and no association was detected in the controls. Using C_{19} binding techniques, Oldstone et al. have shown high frequency of immune complexes in the sera of ALS patients in the continental United States. There was evidence of immune complex deposition in some of the kidneys of the ALS patients. The nature of these immune complexes was not determined. Studies of hepatitis B in the South Pacific reveal that hepatitis B virus is endemic in most of the Pacific Islands. There is high prevalence of hepatitis B surface (HBsAg) antigenemia, and most of the population has either HBsAg or antibody to HBsAg. It is common to have found both HBsAg and anti-HBsAg in many individuals in the population. Since immune complexes are known to cause immunosuppression, we investigated the prevalence of HBsAg, anti-HBsAg, and the immune complexes due to HBsAg and anti-HBsAg in the sera of ALS and PD patients from Guam and healthy controls. Additionally, we also tested sera for the presence of hepatitis A antibody. The data showed that ALS patients have lower levels of anti-HBsAg than PD patients or controls. There was no signficant HBs antigenemia or immune complexes in ALS and PD patients and controls. Almost all sera tested had antibodies to hepatitis A. These studies show that HBsAg and anti-HBsAg complexes were not responsible for the immunosuppression observed. The lower rates of HBsAg in this population may be due to sampling of older individuals.

In other areas of Micronesia, human biological field and laboratory studies continue. Studies of chronic respiratory diseases indicate that 75% of the

children under five years of age were found to have asthma, while over 50% of the adults over 40 years of age were affected by chronic bronchitis, often with an asthmatic component, and typical chronic obstructive airway disease occurred in almost one-third of the male population over 50 years of age. As a result, pulmonary airway diseases constitute the most important cause of morbidity and mortality in the Western Caroline Islands.

CHRONIC ENCEPHALITIS AND EPILEPSY

Since chronic inflammatory neurological disease is known to follow togavirus (arbovirus) encephalitis infections of humans in Europe and Asia, sera from more than twenty American patients with chronic epilepsy and inflammatory brain disease were examined by hemagglutination for all togaviruses known to cause encephalitis of humans in North America. None had antibodies. It seems unlikely that togavirus encephalitis is an important cause of chronic inflammatory brain disease in the United States.

A survey of togaviral antibodies in several Pacific populations confirmed earlier studies of the geographic distribution of several viruses. A possible correlation between susceptibility to Ross River Virus and one red cell Rh subtype was found in a population of Papua New Guinea. Plaque and microtiter tests have been developed for groups A and B togaviruses, and neutralization tests are being performed on selected sera.

SCHIZOPHRENIA AND JUVENILE AUTISM

Serum and CSF specimens from schizophrenic patients and age- and sex-matched controls were obtained from Doctors Torrey and Wineberger of St. Elizabeth's Hospital, Washington, D.C. and Constantine Sakkles of the University of Maryland Hospital, Baltimore. These specimens were tested for group A and group B arboviruses using the hemagglutination inhibition test. Viral antigens used in the test were Eastern and Western Encephalitis, St. Louis encephalitis, and California encephalitis. There was no significant association of arboviral antibodies to schizophrenia. In the light of recent reports by Tyrell, et al., of detection of cytopathic agents from the CSF and some controls, attempts will be made to do similar studies with the CSF samples on hand.

The work on the development of animal models for the study of persistent infections has continued. A foamy virus of chimpanzees (Pan 1, also called foamy virus 6) was isolated in this laboratory over ten years ago. In the chimpanzee it appears to be a latent virus, and can at times be isolated from brain explants of healthy animals. The mechanism of viral latency has been impractical to examine, however, due to the expense and scarcity of the chimpanzee for experimental purposes. Therefore, experiments were conducted to adapt Pan 1 virus to a more convenient laboratory host, and after several preliminary studies, we succeeded in adapting the virus to the mouse. Using kidney and spleen explants from mice-infected neonatally, infectious virus has been isolated up to one month following inoculation, viral antigen has been demonstrated in the explants, and serum CF antibody has been detected. However, in no animal has it been possible to detect infectious virus or viral antigen directly in the organs themselves. We are currently studying the possibility of viral persistence for up to a year following inoculation, and evaluating the mice for any signs of disease during their natural lifetime. Integration of

viral genome in the host cells is also under investigation in collaboration with Dr. Chev Kidson in Australia.

The model of lysogenicity and of subviral genetically active macromolecular structures from the study of bacterial viruses and bacterial genetics supply ample imaginative framework for an expression of our ideas of possible pathogenic mechanisms for kuru and CJD in man. The unconventional viruses of the spongiform encephalopathies tax even our imagination in relation to molecular biology gained from these studies in bacteria.

For a now-disappearing disease, kuru, in a small primitive population to have brought us this far is ample reason for pursuing intensively the challenges offered by the still inexplicable high incidence and peculiar profusion of different neurological syndromes, pathologically distinct yet apparently related to each other, which have been discovered in the several small population enclaves we have investigated. Thus, the high incidence of ALS, ALS-PD on Guam and among a small population of people in West New Guinea, coupled with the high incidence of ALS on the Kii Peninsula of Japan, may indeed offer the best opportunity of solving the problem of this sclerosing disease which in the United States has an incidence as high as that of multiple sclerosis.

The delineation of infection as the etiology of heredofamilial and presenile and senile dementias of man was made possible only through the concomitant studies on the neurobiology of population isolates. In this area we have been engrossed in the investigation of deaf-mutism, mental subnormality and other congenital central nervous system defects associated with endemic goiter in the Central Highlands of Western New Guinea, as well as patterns of delayed puberty, slow growth rates, and of early aging in isolated Melanesian groups. Ethnic drug abuse (particularly of kava), strange patterns of psychosexual development, pseudohermaphroditism, and culturally-determined responses to pain, and roots of aesthetic expression, have all been under study. Foci in primitive population isolates of familial periodic paralysis, progressive muscular dystrophy (both the pseudohypertrophic type of Duchenne and the non-pseudohypertrophic distal type), amyotrophic lateral sclerosis and Parkinsonism, are also being investigated. Genetic studies on human evolution led to the discovery of new genetic factors among haptoglobin, hemoglobin, and red cell enzyme pleomorphisms and the definition of their biochemical structure.

A NEW FORM OF CYSTICERCOSIS EPILEPSY IN MAN AND A NEW SEROLOGICAL TEST FOR CYSTICERSOSIS

The further significance of scientific investigations of small population enclaves of remote populations was even more dramatically apparent during recent field trips of the Chief of LCNSS, with his re-evalaution of what may turn out to be one of the largest "epidemics of epilepsy" ever recorded. This continues to occur in the Wissel Lakes area of West New Guinea and is the result of cysticercosis, an infestation with the larvae of Taenia solium, the pig tapeworm, newly introduced into New Guinea. Our recent studies have led us to conclude that the natural history of this cysticercosis epilepsy is not a result of death of the worm, scarring and calcification of lesions, as much of the literature suggests, but is an early sign of inflammation from new invasion of the brain by the Taenia larvae. After one, two or three grand mal seizures no further convulsions occur and most patients are left without sequellae. Two patients who have died had the most heavily infected brains ever seen, still had

fresh uncalcified cysts, further confirming the thesis that the self-limited seizures result from primary invasion of the larvae and not from old calcified cysts breaking down. Convulsions often occur even before the first subcutaneous nodules appear, and as the nodules increase in number, additional seizures occur. The high incidence of severe third-degree burns, which may even result in death, is a direct result of cysticercosis-induced seizures that occur during sleep, throwing the patient into the house fire. The unclothed people, living at a 2000 meter elevation, need to sleep close to the home fires on cold nights. We are able to date the first introduction of Taenia solium into the area and to plot the spread of taeniasis in pigs and man, and of cysticercosis and associated epilepsy in man, to other previously Taenia-free areas. During this year, we have learned that the cysticercosis has spread both in swine and man throughout the West New Guinea Highlands and is now in the Baliem region. With Dr. Budi Subianto, the local Indonesian medical officer, a visiting scientist in our laboratory, we have planned a neuroepidemiologic study aimed at elucidating the natural history of the epilepsy and acute psychoses and other neurological complications that have occurred concomitantly with the emergence of subcutaneous cysticercosis nodules.

Recently, we developed an enzyme-linked immunoabsorbent (ELISA) serological test for diagnosis and seroepidemiological surveillance of cerebral cysticercosis. Sera collected from adjacent populations prior to the introduction of T. solium and in 1974 and 1977 from patients with epileptic seizures, subcutaneous nodules, and other manifestations of cysticercosis at the Enarotoli hospital were studied. Positive control sera and cerebrospinal fluid (CSF) were from patients with neurocysticercosis in Mexico: their clinical disease had been previously confirmed by the presence of complement-fixing antibodies to cysticercus antigens. For the ELISA test cysticercus antigens were high speed supernatant of a sonicated 20% suspension of cysticerci dissected from Balinese pigs killed in Jakarta; control antigens were similarly prepared from normal pig tissues. The ELISA procedure was that of Voller and Bidwell (1975) and Yolken et al. (1977) for rota virus assays. Titers were expressed as ratio of highest dilution of serum bound by cysticercus antigen to that bound by control antigen of same protein content. Standardization was done using antisera prepared in rabbits injected with cysticercus antigen in complete Freund's adjuvant. In symptomatic patients 5 of 6 (83%) with skin nodules, 7 of 9 (78%) with convulsions and skin nodules, and 7 of 16 (44%) new epileptics without skin nodules had antibody while among non-symptomatic residents of the Wissel Lakes area 4 of 52 (8%) had antibody. None of the 281 sera collected from people outside of the Wissel Lakes area had cysticercus antibody. Among the specimens from Mexican patients with neurocysticercosis 11 of 14 (79%) of the sera and 20 of 25 (80%) of CSF had antibody with geometric mean titers of 580 and 1600, respectively.

Higher percentage of positive patients with systemic cysticercosis may possibly be due to exposure to a larger antigenic mass. The lower positive rates observed among cerebral cysticercosis patients may be due to lack of antibody response due to direct massive infection of the brain by the parasite and short incubation period prior to detection of convulsions. The importance of cerebral cysticercosis in the third world countries cannot be underestimated. The ELISA test provides a simple, sensitive technique adaptable to field use for determining the presence and magnitude of human infections with cysticercus. However, cross reactivity has been observed to occur with antibodies to other parasitic diseases. This has led to studies on the development of techniques to

produce purified cysticercosis antigens for enhancement of the specificity of the reactions. Column-purified and unpurified antigens prepared from either cyst or whole-worm specimens have been tested on a battery of sera from patients with cysticercosis, other parasitic diseases, and normal controls. The results indicate that unpurified whole worm preparations, which are easily available, are satisfactory for most screening purposes, but that purified cyst preparations should be used in situations where schistosomiasis (and, to a degree, echinococcosis) needs to be eliminated from diagnostic consideration. Collaborative studies with physicians in India, Bolivia, and Bali, Indonesia are in progress.

From the standpoint of basic immunology column chromatofocusing and isoelectrofocusing techniques have revealed the identity of a group of proteins responsible for the immunogenic properties of both the cyst and whole worm preparations, and these are currently being further characterized.

VILYUISK ENCEPHALOMYELITIS IN IAKUT PEOPLE OF THE SOVIET SIBERIA: An Old Chronic Infective Degenerative Disease of the CNS New to Western Medicine

As previously reported, the Chief of LCNSS was invited by the Soviet investigators to participate in the investigations in the U.S.S.R. of a unique degenerative disorder of the nervous system, Vilyuisk encephalitis. This disease occurs only in the Iakut region of Eastern Siberia and has many features of a slow virus disease. In 1978 he finally saw and examined patients flown to Moscow. In August 1979 a field study in Iakutia was completed, the first by any western investigator, and many patients with VE were seen throughout the Iakut area. Pathological specimens have been obtained and extensive case records and photographic documents are being analyzed. The diseases of Siberia and the last two decades of Soviet work on the disease, which is clearly infectious, were reviewed. We shall continue our collaborative study of this disease with our Soviet colleagues and we are in the process of writing for publication extensive reports on our field studies and laboratory investigations.

SPINOCEREBELLAR DEGENERATIONS IN HIGH INCIDENCE IN IAKUT PEOPLE OF SOVIET SIBERIA AND IN LES PETIT BLANCS DES HAUTS OF ILE DE LA REUNION, INDIAN OCEAN

In 1981 the Chief of LCNSS completed a second field visit to Ile de la Reunion in the Indian Ocean where we have encountered foci of high incidence spinocerebellar diseases, including a variant of Friedreich's ataxia, another of Marie's spinocerebellar degeneration, and a third of Ramsey Hunt disease occurring exclusively in the "les petits blancs des hauts", very highly inbred descendents of the first French settlers on this previously uninhibited island some three centuries ago.

Among Iakut people of Soviet Siberia there is a huge collection of genetically determined Marie's type of spinocerebellar degeneration which we (DCG) have had a chance to see and study in the field with Dr. Prokopii Petrov and Dr. Lev Gertsovich Goldfarb.

In view of the transmissibility to laboratory primates of familial, apparently dominant genetically determined forms of CJD and of the Gerstmann-Straussler syndrome, we are very interested in these other spinocerebellar degenerations. They are being studied for possible transmissibility and from the possibility of providing a series of pleomorphic

alleles determining cerebellar degenerations of differing forms at various times of life. We hope to parallel some of the studies of the Barbeau Canadian group studying Friedreich's ataxia in Quebec, which differs somewhat clinically from the syndrome on la Reunion.

HEMORRHAGIC FEVER WITH RENAL SYNDROME

During the period covered by this report significant progress has been made on our studies begun in 1953 on the hemorrhagic fevers with renal syndrome that severely affected United Nations troops during the Korean War and for which an etiologic agent had not been isolated in spite of enormous efforts on the part of the Walter Reed Army Institute of Research of which we were then a part. The isolation by Lee and Lee in 1978 of the viruses responsible for HFRS has provided us the opportunity to reinvestigate this disease, characterize the virus and carry out collaborative studies with colleagues in China, the USSR, Finland, Sweden, Yugoslavia, Japan and Korea. In our first review of hemorrhagic fever with renal syndrome Gajdusek in 1953 indicated that clinical severity, particularly hemorrhagic manifestations, of this chronic viral nephropathy varies from one geographic region to another. We suggested that nephropathia epidemica (NE) of Scandinavia was a mild form of HFRS or Korean hemorrhagic fever (KHF) with no or very minimal hemorrhagic manifestations. Mortality in the Far East (China, Korea, USSR) ranges from 5-30%, in European USSR it is lower, while NE is rarely fatal. The sylvatic reservoir for the virus in Scandinavia and European USSR is in wild voles (Clethrionomys sp.), whereas in Eastern Asia it is in the field mouse (Apodemus agrarius). The rat, Rattus rattus, appears to be the reservoir in Japan and in urban foci in Korea. Laboratory rats in Japan and Belgium are infected and have caused HFRS in laboratory workers. The seasonal occurrence varies. Thus, cases are most frequent in the late fall and winter in Scandinavia at a time when wild voles enter dwellings and granaries. In southern and central China cases are more frequent in the autumn, during threshing season, and epidemiology has incriminated the respiratory route of infection. In both East and West sporadic cases occur yet epidemic outbreaks are frequent. This seems to be determined by the particular circumstances of exposure to the rodent reservoir. The military experiences in the Soviet Far East, Manchuria, and Korea of the Russian, Japanese, and United Nations armies, respectively, indicated two epidemic peaks, the first in late spring and early autumn, and the second in late summer and early fall; this was taken to suggest mite- or chigger-borne infection, as is the case with Tsutsugamushi disease. Lee, however, has not found virus in ectoparasites collected from infected rodents. The virulence, as evidenced by hemorrhagic manifestations, systemic reaction and mortality varies as one moves from Far Eastern Asia to eastern and northern Europe. This parallels the shift of virulence of tick-borne encephalitis across the Eurasian landmass. However, Japanese cases are less severe, resembling NE more than KHF; possibly, the virus in rats is less virulent for man. Detailed serological comparisons of strains isolated in different regions are necessary to establish the closeness or divergence of the etiological viruses in various foci, and recent adaptations of the virus to laboratory rats, athymic nude mice, and tissue culture have now made this possible.

The first clear-cut evidence that hemorrhagic fever with renal syndrome virus infections were occurring by the respiratory route stems from the large outbreak of laboratory infections in Moscow in 1962 with 83 affected laboratory

workers. A more recent epidemiological study of infections in medical research laboratories in Japan and Belgium have indicated a respiratory route of infection of laboratory workers working in animal experimental rooms in contact with enzootically silently infected commercially reared white rats. Epidemiological studies in outbreaks in China (Xu et al., 1979) also led to the conclusion that most infection was by contaminated aerosols. Clinical and epidemiological studies in Scandinavia, Hungary, the Soviet Far East and Korea failed to directly incriminate the respiratory route of infection. But exposure to urine and feces contaminated foodstuffs and aerosols, or arthropod vectors, and ectoparasites such as mites and chiggers, on infected rodents were usually thought to be the source of human infection. However, it is now evident that infection occurs most often by the respiratory route from contaminated aerosols produced by the asymptomatically infected reservoir rodents. Whether saliva and respiratory droplet infection--the only secretions from which virus has been isolated--is the only source of such aerosol contamination remains to be proved. Finally, high titer antigen has been found only in the lungs in infected wild mice (Apodemus agrarius), voles (Clethrionomys glareolus), wild urban rats (Rattus rattus), and laboratory rats of the Wistar strain in Japan; other tissues contain lower concentrations of antigen as demonstrated by immunofluorescence. In experimentally infected white rats (Wistar and Fischer strains) and athymic nude mice the virus also appears in highest concentration in the lungs. The virus has to date been isolated only from lung, saliva, throat washings and blood of human patients, and no other tissue or secretion has yet been found to be infectious. In naturally and experimentally infected rodents the virus has not to date been isolated from feces or urine, but it has been obtained regularly from lung, saliva, and acute phase blood.

Until recently, the serological relationship between Scandinavian nephropathia-epidemica (NE) and Korean hemorrhagic fever (KHF) has been established (Svedmyr, 1978; Lahdevirta, 1979). This was first done using only as antigen KHF virus propagated in the lungs of naturally and experimentally infected Apodemus agrarius mice. We have recently confirmed this antigenic relationship by demonstrating specific neutralizing antibody to KHF virus in convalescent sera from patients with NE. Similar relationships have been shown for HFRS in European Russia with KHF virus. However, until the European virus was isolated from NE in Finland, it was previously impossible to check for immunological crossings in both directions. This has now been done and it is clear that NE sera react with Korean antigen in the immunofluorescent tests at almost the same titers with the homologous antigen from naturally infected or experimentally infected Clethrionomys lung. KHF human sera, on the other hand, give much higher titers with the homologous Korean virus in Apodemus lung than with the Finnish virus in Clethrionomys lung. Sera from patients convalescent from HFRS in southern and central China react by immunofluorescence similarly to KHF sera as sera from HFRS patients in the Soviet Far East and in Japan. All these Asian sera (Chinese, Soviet, Korean and Japanese) from HFRS patients as well as Scandinavian NE sera neutralize several $\log_{10}$ of KHF virus but qualitative cross neutralization tests have not yet been possible since the NE agent is only propagated with difficulty in Clethrionomys voles. Thus, the serological crossing is a partially one-way cross, with KHF sera reacting at 10- to 20-fold lower titer with NE antigen than with the homologous antigen, while, in contrast, Scandinavian NE sera show only a 2-fold reduction in titer with lung from Apodemus or nude mice infected with KHF than with the homologous antigen in Clethrionomys lung. Where in crossing Soviet Eurasia the shift to the NE from the KHF serological type occurs, remains to be determined. Sera

from Balkan (Czechoslovakia, Hungary, Bulgaria, Rumania, and Yugoslavia) cases of HFRS are now available for such study. We have demonstrated closer serological relationships with NE than with KHF in Yugoslavia sera from HFRS patients, in keeping with the geographic shift of the serotype from Asia to Europe.

In a previous report (XIV Pacific Science Congress, 1979) we conjectured about the possible presence of unrecognized hemorrhagic fever with renal syndrome (HFRS) in North and South America and other areas of the world wherein the disease had not previously been recognized. The natural host of HFRS in northern and eastern Europe, Clethrionomys sp., is indigenous across northern North America in Canada and the United States from Maine to Alaska. The murine host of the virus of Korean hemorrhagic fever (KHF), Apodemus sp., is not found in the Americas. Clethrionomys-borne disease in Europe has proved to be less severe clinically, and demonstrates fewer hemorrhagic symptoms than the Apodemus-borne disease in eastern Asia (China, USSR, and Korea). Thus, a milder form of nephropathy associated with little or no hemorrhagic diasthesis, as in nephropathia epidemica (NE) in Scandinavia, might be expected in the Americas. Using the indirect immunofluorescence test for demonstrating specific antigen-antibody reactions in KHF infections we have tested sera from Alaska, South America, Iran, and India. In the first 100 sera we studied from Alaska we reported no antibodies to KHF virus; however, when this series was extended to 600 specimens a single serum had specific antibody to KHF virus at titer 1:128. We also tested 4 cerebrospinal fluids (CSF) and 16 convalescent sera from children with an undiagnosed acute febrile illness in Santa Cruz, Bolivia. Although none of the 4 CSF reacted, 2 of the 16 sera had antibody titers to KHF virus of 1:256 and 1:128, respectively. Of 251 sera from residents of remote rural villages in India, 2 had antibodies to KHF virus; a 35-year old male gardener and a 27-year old female with titers of 1:256 and 1:640, respectively. Casals has found (personal communication) that high titering specific antibody to KHF virus failed to react in the HAI test against Japanese B, Murray Valley, Omsk hemorrhagic fever, and Chikungunya antigens. We found that high titering rabbit antisera or mouse ascitic fluids to more than 30 arboviruses, including Rift Valley fever and Junin viruses, and antisera to simian hemorrhagic fever virus did not react with KHF virus in the IF test. No other viruses are known to cross react with HFRS by the IF test. Neutralization tests on the few positive sera we have found from Alaska, Bolivia and India are in progress. These preliminary data suggest a possible wider distribution of HFRS viruses than is now known and further seroepidemiological screening from other parts of the world is clearly needed.

GENETIC EFFECTS ON SUSCEPTIBILITY TO ARBOVIRUS INFECTION

Continuing our more than three decades on work on the arthropod-borne viruses we have this year completed a study on human variation and infection with these viruses in humans in New Guinea. Antibodies to group A (Chikungunya, Getah, Sindbis, Ross River) and group B (dengue 2 and 4, Murray Valley encephalitis, Japanese encephalitis, Yellow fever, Zika) arboviruses were measured by hemagglutination inhibition and neutralization in sera from selected aboriginal populations of New Guinea. Antibodies to Murray Valley encephalitis and Ross River viruses were highly prevalent in most of the lowland populations. For each population the presence of antibodies was correlated with 12 genetic polymorphic systems: 7 blood groups (ABO, MN, Ss, Rh, P, Kidd, Duffy), 3 red

cell enzymes (acid phosphatase, 6-PGD, PGM), and ? serum proteins (haptoglobin and immunoglobulin Gm).

There were no significant associations between any marker system and Murray Valley encephalitis virus infection. For one population, two blood group systems, Rh and Kidd, showed statistically significant associations with antibodies to the Ross River virus. Among individuals with the Rh phenotype R_1R_0 (CcDee), the relative risk of infection with Ross River virus was five times less than that for other members of the population. The relative risk of Ross River virus infection in individuals with Kidd phenotype Jka- was approximately three times less than that of the Jka+ individuals.

The reasons for those associations are unknown. Hypothetical explanations include differences in cell membranes of some Rh and Kidd phenotypes impeding attachment of virus, hereditary impairment of immune responses to the virus, shared antigens between the virus and blood-group substances resulting in immune tolerance, and decreased biting by mosquitoes of individuals with particular phenotypes. It is also possible that some genetically related social subgroup of people with less exposure to mosquitoes exists in the population. The associations between Rh and Kidd phenotypes and susceptibility to group A or other arthropod-borne infections must be confirmed by studies of larger populations living where such infections are endemic.

The development and maturation of the two major projects of this laboratory have resulted from cross-fertilization of each since their origin, and both have grown from the basic studies on child growth and development and disease patterns in primitive cultures. Although the two projects, each composed of many subsections, differ markedly in the questions they address and the techniques of investigation they employ, much of the field data collected from one project is also requisite for the studies in other projects. Both are served by the same investigators, who function as a team. These scientists derive their creative stimulus, dedication and enthusiasm to a great extent from the atypical and exotic biological, social and cultural materials presented, and the diverse, frequently unconventional, approaches of the two projects.

Principal Investigators: D. Carleton Gajdusek, M.D.
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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01282-18 CNSS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Neurobiology of Population Isolates: Study of Child Growth and Development, Behavior and Learning, and Disease Patterns in Primitive Cultures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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12	8	4

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Studies of human biology of vanishing primitive societies focus on neurological development and learning patterns in diverse cultural experiments in the human condition found in such isolated groups. Laboratory studies by molecular biology, immunology, virology, and biochemistry on specimens and field epidemiological work in these genetically isolated primitive bands give less complicated bare-line data than obtainable from civilized societies. Data and specimens collected over years on expeditions to Micronesia, Polynesia, Solomon Islands, New Hebrides, New Guinea, Indonesia, S. America, Asia and Africa are used. Studies on nutrition, reproduction, fertility, neuroendocrine influences on age of sexual maturation and aging, genetic polymorphisms, genetic distance, unusual and odd employment of the higher cerebral CNS function of language learning, cognitive styles, computation (calculation without words or numbers) and culturally modified sexual behavior elucidate alternative forms of neurologic functioning for man which we would be unable to investigate once the natural cultural experiments in primitive human isolates were amalgamated into the cosmopolitan community of man. Foci of high incidence prevalence of kuru, ALS/PD, epilepsy, other neurological degenerations, hysterical disorders, schizophrenia, neoplasms, goiter, cretinism, rheumatoid diseases, diabetes, asthma, chronic lung disease, malaria, filariasis, leprosy, cysticercosis and other infections are investigated.

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YUGOSLAVIA: Prof. J. Vesenjak-Hirjan, Sveucilistau Zagrebu, Zagreb.

Sub-Project I:	Study of the development patterning of the human nervous system (cybernetics of human development).
Sub-Project II:	Human evolutionary studies in isolated primitive groups.
Sub-Project III:	Studies of isolated Micronesian populations.
Sub-Project IV:	Studies of isolated New Guinea populations.
Sub-Project V:	Studies of Australian Aborigines.
Sub-Project VI:	Studies of isolated New Hebrides and Solomon Islands populations.
Sub-Project VII:	Studies of Central and South American Indians.
Sub-Project VIII:	Developmental, genetic and disease patterns in primitive populations of Asia, Africa, Indonesia, Melanesia, Micronesia, Polynesia and the Arctic.
Sub-Project IX:	Experimental developmental neuropediatrics in infantile programming: a empirical approach to the language of information input into the nervous system.
Sub-Project X:	Ciphers and notation for the coding of sensory data for neurological information processing.
Sub-Project XI:	Racial distribution and neuroanatomic variations in the structure of the human brain.
Sub-Project XII:	Studies of high incidence of neurological disease in specific racial and ethnic groups and in primitive or geographic population studies.

Project Description: Neurobiology of Population Isolates: Study of Child Growth and Development, Behavior and Learning, and Disease Patterns in Primitive Cultures (are attached)

Publications: Listed on pages 43 - LCNSS/IRP through 54 - LCNSS/IRP

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 00969-18 CNSS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Chronic CNS Disease Studies: Slow, Latent and Temperate Virus Infections

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PRINCIPAL INVESTIGATORS: D. Carleton Gajdusek, M.D., Chief, LCNSS; and Clarence J. Gibbs, Jr., Ph.D., Deputy Chief, LCNSS

OTHER: Herbert L. Amyx, D.V.M.; David M. Asher, M.D.; Sina Baymanyar, M.D.; Maria-Teresa Borras, Ph.D.; Paul W. Brown, M.D.; Marie-Claude Moreau-Dubois, Ph.D.; Ryo Fukatsu, M.D.; Ralph M. Garruto, Ph.D.; Yasuo Kuroda, Ph.D.; Pyung-Woo Lee, Ph.D.; Maryellen F. Masciangelo, Ph.D.; Maurizio Pocchiari, M.D.; Robert G. Rohwer, Ph.D.; Richard T. Yanagihara, M.D.; Francoise Cathala, M.D.; Dimitry Goldgaber, Ph.D.

COOPERATING UNITS (if any) AUSTRALIA: Dr. Byron A. Kakulas, University of Western Australia, Nedlands; Dr. Chev Kidson, Queensland Institute of Medical Research, Brisbane; Dr. Robert L. Kirk, Australian National University, Canberra; Dr. Ian MacKay, Royal Melbourne Hospital, Melbourne; (continued)

LAB/BRANCH
Laboratory of Central Nervous System Studies, Intramural Research Program

SECTION

INSTITUTE AND LOCATION National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
24	14	10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Studies elucidate cause and pathogenesis of chronic degenerative CNS disorders with emphasis on MS, ALS, parkinsonism-dementia, Parkinson's, Pick's, and Alzheimer's disease, Huntington's chorea, supranuclear palsy, other presenile dementias, chronic encephalitis with focal epilepsy, muscular dystrophies, chronic schizophrenia, SSPE, PML, dialysis encephalopathy, and intracranial neoplasms. Even familial, apparently hereditary diseases may be slow virus infections. Subacute spongiform virus encephalopathies (kuru and Creutzfeldt-Jakob (CJD) disease of man; scrapie and mink encephalopathy) are caused by unconventional viruses with unique properties posing important theoretical problems to microbiology and molecular biology; a major goal is elucidation of their structure and mechanisms of replication. Transmissible virus dementias are increasingly recognized worldwide causes of death: high incidence foci, transmission by corneal transplant or brain surgery, and occupational hazards from exposure to brain occur. In order to determine the usual mode of infection with the virus, a worldwide epidemiological study of transmissible virus dementia (CJD) cases is underway with special attention to familial clusters of cases and with a quest for possible relationship of scrapie of sheep to the human disease.

COOPERATING UNITS: (continued)

AUSTRALIA: Dr. Colin Masters, University of Western Australia, Perth; Dr. Eric Shaw, Red Cross Blood Transfusion Service, Brisbane; Dr. Vincent Zigas, Sunnybank.

AUSTRIA: Prof. F. Seitelberger, University of Vienna, Vienna.

BELGIUM: Dr. A. Lowenthal, L'Institut Bunge, Antwerp.

CANADA: Dr. John H. Deck, Toronto Western Hospital, Toronto; Dr. Joseph Gilbert, University Hospital, London; Dr. Arthur J. Hudson, University Hospital; London; Dr. Andrew Kertez, St. Joseph's Hospital, London; Dr. Theodore Rasmussen; McGill University, Montreal; Dr. N.B. Rewcastle, Banting Institute, Toronto.

CHILE: Dr. Sergio Galvez, Institute de Neurocirugia, Santiago.

CHINA: Prof. Chi-lu Chen, National Taiwan University, Taipei; Dr. C.H. Yen, National Health Administration; Taipei; Dr. Chin-Yun Yii, Kaohsinung Medical College, Kaohsiung.

CUBA: Dr. Segundo Mesa-Castillo, Hospital Psiquiatrico de la Habana, Havana.

CZECHOSLOVAKIA: Dr. Helena Libokova, Slovak Academy of Sciences, Bratislava; Dr. Vlastimil Mayer, Slovak Academy of Sciences, Bratislavia; Dr. Eva Mitrova, Research Institute for Preventative Medicine, Limbova.

EGYPT: Dr. Harry Hoogstraal, Naval Medical Research Unit, Cairo.

ENGLAND: Mrs. Elisabeth Beck, Institute of Psychiatry, London; Dr. M.C. Clark, Agricultural Research Council, Compton; Prof. P.M. Daniel, Royal College of Surgeons, London; Prof. George Dick, Regional Dean's Office, London; Prof. L.W. Duchen, The National Hospital, London; Dr. D.A. Haig, Agriculture Research Council, Compton; Dr. Gordon D. Hunter, Agricultural Research Council, Compton; Prof. W.B. Matthews, University of Oxford, Oxford, Dr. R. Kimberlin, Agricultural Research Council, Compton.

FINLAND: Prof. Nils Oker-Bloom, University of Helsinki, Helsinki.

FRANCE: Dr. Jacques Bert, Centre Hôpital et Universite, Marseille; Dr. Francoise Cathala, Hôpital de la Salpetriere, Paris; Dr. Henri-Pierre Cathala, Hôpital de la Salpetriere, Paris; Dr. Louis Court, Centre de Recherches du Service, Clamart; Dr. Michel Dumas, CHU, Limoges; Prof. A.E. Escourolle, Charles Foix La Salpetriere, Paris; Dr. Henri Gastaut, University de Marseille, Marseille; Dr. Patrick Gourmelon, CRSSA, Clamart; Dr. Raymond Latarjet, Institut du Radium; Paris; Dr. Martin, CHU, Nice; Dr. Francis Rohmer, CHU, Strasbourg; Dr. Michel Samson, CHU, Roen; Dr. Schott, CHU, Lyon; Prof. Tamalet, Hôpital de La Timone, Marseille.

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PAPUA NEW GUINEA: Dr. Michael Alpers, Institute for Medical Research, Goroka.

PERU: Dr. Luis Palomino, Hospital Santo Toribio, Lima.

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SOUTH AFRICA: Dr. J.H.S. Gear, National Institute of Virology, Sandringham.

SPAIN: Dr. J.A. Sanchez-Martin, Instituto de Investigaciones, Madrid; Dr. Alberto Portera-Sanchez, Cuidad Savitaria Primero, Madrid.

SWEDEN: Dr. Erling Norrby, Karolinska Institue, Stockholm; Dr. Arne Svedmyr, Central Bacteriological Laboratory, Stockholm.

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UNITED STATES: California--Dr. J. Richard Baringer, V.A. Hospital, San Francisco; Dr. Ashley T. Haase, V.A. Hospital, Palo Alto; Dr. R. Nick Hogan, V.A. Medical Cednter, San Francisco; Dr. Kenneth P. Johnson, San Francisco; Dr. David E. Kohne, Center for Neurologic Studies, San Diego; Dr. Peter Lampert, University of California, La Jolla; Dr., Edwin H. Lennette, State Department of Health, Berkeley; Dr. Michael N. Oxman, V.A. Hospital, San Diego; Dr. Linus Pauling, Linus Pauling Institute, La Jolla; Dr. Stanley Prusiner, University of California, San Francisco; Dr. Gunther Stent, University of California, Berkeley; Dr. W. W. Tourtellotte, V.A. Hospital, Los Angeles; Dr. Myron Varon, Amyotrophic Lateral Sclerosis Society, Sherman Oaks; Dr. Steven Waxman, Stanford University, Stanford; Dr. Leslie P. Weiner, University of Southern California, Los Angeles. Connecticut--Dr. P. N. Bhatt, Yale University, New Haven; Dr. G.D. Hsiung, V.A. Medical Center, West Haven; Dr. Elias and Laura Manuelides, Yale University School of Medicine; New Haven. Hawaii--Dr. Arwin R. Diwan, University of Hawaii, Honolulu; Dr. Scott B. Halstead, University of Hawaii, Honolulu; Dr. Hong-Yi Yang, University of Hawaii, Honolulu. Illinois--Dr. Raymond A. Classen, Presbyterian-St. Lukes's Hospital, Chicago; Dr. Raymond Roos, University of Chicago, Chicago. Indiana--Dr. Bernadino Ghetti, Indiana University School of Medicine, Indianapolis; Dr. Morris Pollard, Lobund Laboratory, Notre Dame; Dr. A.N. Siakotos, Indiana University, Indianapolis. Kentucky--Dr. Dan Tynan, V.A. Hospital, Lexington. Louisiana--Dr. William Greer, Gulf South Research Institute, New Iberia. Maryland--Dr. Frederick B. Bang, Johns Hopkins University, Baltimore; Dr. Theodore O. Diener, Agricultural Research Center West, Beltsville; Dr. Richard T. Johnson, Johns Hopkins

COOPERATING UNITS: (continued)

University, Baltimore; Dr. David Lang, University of Maryland, Baltimore; Mrs. Meta Neumann, Bethesda: Dr. Robert Traub, University of Maryland, Baltimore; Dr. Charles Wisseman, University of Maryland, Baltimore; Dr. K.V. Shah, Johns Hopkins University, Baltimore; Mr. T.C. Rains, National Bureau of Standards, Gaithersburg. Massachusetts--Dr. Amico Bignami, Children's Hospital Medical Center, Boston; Dr. Bernard Fields, Harvard Medical School, Boston; Dr. E. P. Richardson, Jr., Massachusetts General Hospital, Boston; Dr. W.C. Schoene, Peter Bent Brigham Hospital, Boston. Nevada--Dr. Warren V. Huber, V.A. Medical Center, Reno. New York--Dr. Samuel J. Ayl, The National Foundation March of Dimes, White Plains; Dr. Jordi Casals, Mt. Sinai School of Medicine, New York; Dr. Alfred E. Earle, The Public Health Research Institute, Otisville; Dr. Teresita S. Elizan, Mt. Sinai School of Medicine, New York; Mr. Ernie Green, The New York Public Health Research Institute, Otisville; Dr. Asao Hirano, Montefiore Hospital, Bronx; Dr. John Hotchin, Department of Health, Albany; Dr. J. Moor-Jankowski, New York University Medical Center, New York; Dr. Imaharu Nakano, Montifiore Hospital and Medical Center, New York; Dr. Michael L. Shelanski, New York University Medical Center, New York; Dr. Robert A. Sommerville, New York State Institute for Basic Research in Mental Retardation, Staten Island; Dr. Robert D. Terry, Albert Einstein Medical Center, Bronx; Dr. Roger D. Traub, IBM Thomas B. Watson Research Center, Yorktown Heights; Dr. James D. Watson, Cold Spring Harbor Laboratory, Cold Spring. Ohio--Dr. S.M. Chou, Cleveland Foundation, Cleveland; Dr. Maurice Victor, Metropolitan General Hospital, Cleveland. Pennsylvania--Dr. Milton Alter, Temple University Medical Center, Philadelphia; Dr. Donald Gilden, Wistar Institute, Philadelphia; Dr. Neal Nathanson, University of Pennsylvania School of Medicine, Philadelphia. South Carolina-- Dr. Paul M. Hoffman, V.A. Hospital, Charleston. Texas--Dr. Samuel Baron, University of Texas, Galveston; Dr. Steven Wiesenfeld, Southwest Allergy Service, Midland. Virginia--Dr. J. L. Hourrigan, Arlington. Washington--Dr. Ellsworth C. Alvord, Jr., University of Washington, Seattle. Washington, D.C.--Dr. Harold Booker, Veterans Administration Central Office, Washington; Col. Dan C. Cavanaugh, Walter Reed Army Institute, Washington; Dr. John Kurtzke, V.A. Hospital, Washington; Dr. Frederick C. Robbins, National Academy of Science, Washington; Dr. Fuller Torrey, St. Elizabeth's Hospital, Washington. Wisconsin--Dr. Richard F. Marsh, University of Wisconsin, Madison; Dr. Gabriel Zu Rhein, University of Wisconsin, Madison.

YUGOSLAVIA: Dr. Miha Likar, Mikrobioloski Institut, Ljubljana; Prof. J. Vesenjak-Hirjan, University of Zagreb, Zagreb.

Sub-Project I: Attempts to isolate, identify and characterize transmissible agents from humans and animals with subacute degenerative diseases of the central nervous system: transmissible heredofamilial diseases, presenile and senile dementias of the sporadic and familial types and primary sclerosing and demyelinating diseases.

Sub-Project II: Characterization and pathogenesis of kuru virus.

Sub-Project III:	Characterization and pathogenesis of Creutzfeldt-Jakob disease (transmissible dementia virus).
Sub-Project IV:	Scrapie: studies on the purification, physical and biological characterization and nature of the virus.
Sub-Project V:	In vitro cultivation of the viruses of the subacute spongiform virus encephalopathies in cell cultures.
Sub-Project VI:	Host range of susceptible laboratory animals to the viruses of the subacute spongiform virus encephalopathies.
Sub-Project VII:	Strain variations among the viruses of the subacute spongiform virus encephalopathies.
Sub-Project VIII:	Cell-fusing properties of the viruses of the subacute spongiform virus encephalopathies.
Sub-Project IX:	Resistance to radiation of the viruses of the subacute spongiform virus encephalopathies.
Sub-Project X:	Resistance to disinfectants of the viruses of the subacute spongiform virus encephalopathies.
Sub-Project XI:	Tissue and cell culture techniques used to unmask slow infection of man and animals using brain and viscera biopsy and early autopsy, bone marrow and peripheral leucocyte specimens.
Sub-Project XII:	The syncytium-forming viruses (simian and human foamy viruses).
Sub-Project XIII:	Studies on transformed human brain tissue in vitro and characterization of associated virus.
Sub Project XIV:	Electron microscopic membrane studies of subacute spongiform virus encephalopathies.
Sub-Project XV:	Characterization and identification of new herpes viruses from explant cultures of tissues from subhuman primates.
Sub-Project XVI:	Studies on persistent asymptomatic cytomegalovirus infections of healthy rhesus monkeys.
Sub-Project XVII:	Focal movement disorders in rhesus monkeys following experimental infection with a strain of tick-borne encephalitis virus.

Sub-Project XVIII: Fluorescent antibody studies on the intracellular localization and identification of virus antigens in vivo and in vitro in tissues from patients with subacute diseases of the central nervous system.

Sub-Project XIX: Isolation and characterization of adenovirus from the urine of chimpanzees.

Sub-Project XX: Development of serological and immunological test system for use in the study of slow infections of the central nervous system.

Sub-Project XXI: Immune responsiveness of multiple sclerosis patients to established viral antigens by detection of specific antibodies in serum and cerebrospinal fluids collected serially during remission and exacerbation.

Sub-Project XXII: Animal management and intercurrent diseases in subhumans primates on long-term studies of slow infections.

Sub-Project XXIII: Studies to determine the possible presence of cryptic viral genomes in human brain tissues.

Sub-Project XXIV: Sequential development of kuru-induced neuropathological lesions in spider monkeys.

Sub-Project XXV: Studies on the isolation, characterization, identification and pathogenicity of type C viruses from human and animal tissues.

Sub-Project XXVI: Biochemical studies of the etiology of amyotrophic lateral sclerosis and parkinsonism-dementia.

Sub-Project XXVII: Study of mitochondrial mutants from scrapie-infected mouse brain cells.

Sub-Project XXVIII: Isolation and characterization of the etiological agent of Scandinavian nephro-nephritis epidemica.

Sub-Project XXIX: The pathogenesis of Korean hemorrhagic fever virus and the elucidation of its biological and physical properties.

Sub-Project XXX: Worldwide seroepidemiological evidence of antibodies in human populations to the virus of Korean hemorrhagic fever.

Sub-Project XXXI: Development of an enzyme-linked immunoadsorbent (ELISA) test for the diagnosis and epidemiology of cysticercosis-induced epilepsy.

Sub-Project XXXII: Studies on the cytochemical and morphological properties of neurons cultured *in vitro*.

Sub-Project XXXIII: Development of immunological markers for the detection of autoantibodies to neurofilaments in the sera of patients with subacute spongiform encephalopathies.

Sub-Project XXXIV: Studies to determine the neurophysiological changes of neurons *in vitro* infected with CJD.

Sub-Project XXXV: Effects of the subacute spongiform viruses on nerve cells grown *in vitro*.

Sub-Project XXXVI: *In vivo* and *in vitro* studies to determine the etiology of myasthenia gravis.

Sub-Project XXXVII: Neurophysiological study of animals experimentally infected with subacute spongiform virus encephalopathies.

Project Description: Chronic Central Nervous System Disease Studies (described fully on pages 1-LCNSS/IRP through 27-LCNSS/IRP).

The projects (I through XXXVII) listed herein, as itemized in the Project Reports of previous years, have continued throughout this year and have been expanded, as are reflected in the extensive list of publications and the summary will follow. Contractural phases of this work are being conducted at: Gulf South Research Institute, New Iberia, Louisiana; and Public Health Research Institute of the City of New York, Inc., Otisville, New York.

Publications: Listed on pages 43 - LCNSS/IRP through 54 - LCNSS/IRP

PUBLISHED: Z01 NS 01282-18 CNSS and Z01 NS 00969-18 CNSS

1. Asher, D.M., Masters, C.L., Gajdusek, D.C., and Gibbs, C.J., Jr. (1982) Familial spongiform encephalopathies. In "Genetics of Neurological and Psychiatric Disorders," S.S. Kety, L.P. Rowland, R.L. Sidman, and S.W. Matthysse. Raven Press, New York, pp. 273-291.

2. Bahmanyar, S., Gajdusek, D.C., and Sotelo, J. (1982) Longitudinal spinal cord sections as substratum for anti-neurofilament antibody detecton. Journal of Neurological Sciences, 53:1 (January), 85-90.

3. Beck, E., Daniel, P.M., Davey, A., and Gajdusek, D.C. (1982) The pathogenesis of spongiform encephalopathies: an ultrastructural study. Brain, 105:4, 755-786.

4. Board, P.G., Gibbs, C.J., Jr. and Gajdusek, D.C. (1981) Polymorphism of erythrocyte glyoxalase II in anthropoid primates. Folia primatologica, 36, 138-143.

5. Borras, M.T., Kingsbury, D.T., Gajdusek, D.C. and Gibbs, C.J., Jr. (1982) Inability to transmit scrapie by transfection of mouse embryo cells in vitro. Journal of General Virology, 58: 263-271.

6. Brown, P. (1982) Response to a letter to the editor about the article: An Epidemiologic Critique of Creutzfeldt-Jakob disease. American Journal of Epidemiology, 115:1 (January), 145-151.

7. Brown, P., Cathala, F., and Gajdusek, D.C. (1981) Mycobacterial and fungal skin sensitivity patterns among remote population groups in Papua New Guinea, and in the New Hebrides, Solomon, and Caroline Islands. American Journal of Tropical Medicine and Hygiene, 30:5, 1085-1093.

8. Brown, P., Gibbs, C.J., Jr., Amyx, H.L., Kingsbury, D.T., Rohwer, R.G., Sulima, M.P. and Gajdusek, D.C. (1982) Chemical disinfection of s to Creutzfeldt-Jakob disease virus. New England Journal of Medicine, 306:21 (May 27), 1279-1282.

9. Brown, P., Moreau-Dubois, M.C. and Gajdusek, D.C. (1982) Persistent asymptomatic infection of the laboratory mouse by simian foamy virus type 6: a new model of retrovirus latency. Archives of Virology, 71, 229-234.

10. Brown, P., Rohwer, R.G., Green, E., and Gajdusek, D.C. (1982) Effect of chemicals, heat and histopathologic processing on high infectivity hamster-adapted scrapie virus. Journal of Infectious Diseases, 145:5 (May) 683-687.

11. Cathala, F., Brown, P., Chatelain, J., Raharison, S., Lecanuet, P., Castaigne, P., Gibbs, C.J., Jr. and Gajdusek, D.C. (1982) Maladie de Creutzfeldt-Jakob en France: contribution a une recherche epidemiologique. Revue Neurologique (Paris), 138:1, 39-51.

12. Cathala, F., Court, L., Breton, P., Mestries, J.C., Gourmelon, P., Dormont, D., Lemercier, M., Gray, F., Hauw, J.J., Escourolle, R., Gibbs, C.J., Jr. and Gajdusek, D.C. (1981) La maladie de Creutzfeldt-Jakob experimentale du singe ecureuil. Revue Neurologique (Paris), 137:12, 785-805.

13. Chatelain, J., Cathala, F., Brown, P., Raharison, S., Court, L., and Gajdusek, D.C. (1981) Epidemiologic comparisions between Creutzfeldt-Jakob disease and scrapie in France during the 12 year period 1968-1979. Journal of the Neurological Sciences, 51;3, (September), 329-337.

14. Coker-Vann, M., Subianto, B., Brown, P., Diwan, A., Desowitz, R., Garruto, R.M., Gibbs, C.J., Jr. and Gajdusek, D.C. (1981) ELISA antibodies to cysticerci of Taenia solium in human populations in New Guinea and Southeast Asia. Southeast Asia Journal of Tropical Medicine and Public Health, 12:4 (December), 499-505.

15. Coker-Vann, M., Subianto, B., Brown, P., Diwan, A., Desowitz, R., Garruto, R.M., Gibbs, C.J., Jr. and Gajdusek, D.C. (1981) ELISA antibodies to cysticerci of Taenia solium in human populations in New Guinea and Southeast Asia. Southeast Asia Journal of Tropical Medicine and Public Health, 12:4 (December), 499-505.

16. Diwan, A., Coker-Vann, M., Brown, P., Subianto, D.B., Yolken, R., Desowitz, R., Escobar, A., Gibbs, C.J., Jr. and Gajdusek, D.C. (1982) Enzyme-linked immunosorbant assay (ELISA) for the detection of antibody to cysticerci of Taenia solium. American Journal of Tropical Medicine and Hygiene, 31:2 (March), 364-369.

17. Doi, H., Tateishi, J., Ohta, M., Kuroiwa, Y., Gajdusek, D.C., Chen, K.-M., and Gibbs, C.J., Jr. (1982) Neuropathological study of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam: an analysis of 24 autopsy cases. Brain and Nerve, 34:1 (January), 63-70.

18. Franko, M.C., Koski, C.L., Gibbs, C.J., Jr., McFarlin, D.E., and Gajdusek, (1982) Monoclonal P_0 protein-specific antibody: derivation and characterization. Proceedings of the National Academy of Science, 79:11 (June), 3618-3622.

19. Franko, M.C., Masters, C.L., Gibbs, C.J., Jr. and Gajdusek, D.C. (1981) Monoclonal antibodies to central nervous system antigens. Journal of Neuroimmunology 1:4 (December), 391-411.

20. Gajdusek, D.C. (1982) Hemorrhagic fever with renal syndrome (Korean hemorrhagic fever, epidemic hemorrhagic fever, nephropathia epidemica): A newly recognized zoonotic plague of Eurasian landmass with the possibility of related infections on other continents. Abstract number 5E-2 in "Programme and Abstracts of the International Seminar on Viral Diseases in South-East Asia and the Western Pacific," Australian Academy of Science, Canberra, February 8-12, p. 21.

21. Gajdusek, D.C. (1982) Viral infections in childhood in southeast Asia and the western Pacific. Abstract number 1-5 in"Programme and Abstracts of the International Seminar on Viral Diseses in South-East Asia and the Western Pacific," Australian Academy of Science, Canberra, February 8-12, p. 2.

22. Gajdusek, D.C. (1982) Editorial in the Papua New Guinea Medical Journal on Huntington's Chorea. Papua New Guinea Medical Journal, 25:1, (March), 1-2.

23. Gajdusek, D.C. (1982) Hemorrhagic fever with renal syndrome (Korean hemorrhagic fever, epidemic hemorrhagic fever, nephropathia epidemica): A newly recognized zoonotic plaque of the Eurasian landmass with the possibility of relative muroid virus nephorpathies on other continents. In "Viral Diseases in South-East Asia and the Western Pacific," J.S. Mackenzie, editor. Academic Press, Sydney, pp. 576-594.

24. Gajdusek, D.C. (1982) Viral infections in childhood in South-East Asia and the Western Pacific. In "Viral Diseases in South-East Asia and the Western Pacific," J.S. Mackenzie, editor. Academic Press, Sydney, pp. 77-78.

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TAB 10 -- LABORATORY OF MOLECULAR BIOLOGY -- LMB/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Molecular Biology
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Molecular Biology
National Institutes of Neurological and Communicative Disorders and Stroke

Ernst Freese, Chief

The Laboratory has unraveled the physiological processes controlling the initiation of differentiation (sporulation) in bacteria and of meiosis and the resulting sporulation in yeast. Use of these organisms has the advantage that their genetic and biochemical properties are most thoroughly known among all differentiating organisms. The Laboratory has also used this knowledge to isolate and characterize the gene for a developmental enzyme. Studies in mammalian cells and mouse embryos have revealed the appearance of developmental proteins and the role of insulin in the coupling of an extracellular receptor to the intracellular messenger.

1. Molecules controlling bacterial differentiation (sporulation). Differentiation of microbes and embryonic cells is generally initiated by nutritional deprivation. In Bacillus subtilis, the Laboratory has demonstrated that massive differentiation (sporulation) is observed only when the concentration of guanosine triphosphate (GTP) decreases below a critical value. This can be achieved by partial nutritional deprivation or by the "stringent response" which results from partial amino acid deprivation and is accompanied by the increase of ppGpp. More specifically, it can be produced by inhibitors of guanosine monophosphate (GMP) synthesis, or by the deprivation of GMP in guanine auxotrophs. In contrast to the normal stringent strains, relaxed (rel) mutants did not sporulate as a result of partial amino acid deprivation. Certain antibiotics (e.g. chloramphenicol, fusidate, kasugamycin, etc.) also prevented the sporulation resulting from the stringent response when they were used at concentrations at which they did not significantly inhibit growth. In all these cases, sporulation was restored when GMP synthesis was directly inhibited, e.g., by the addition of decoyinine. The effect of GTP deprivation on various cellular processes was compared with the effect of partial UTP deprivation, which does not initiate sporulation. Both deprivation conditions caused a drastic decrease in the synthesis of rRNA and tRNA and an increase (derepression) in the synthesis of some nucleotide degrading enzymes, but they had only a small effect on the synthesis of mRNA. Specific effects were observed for changes in membrane transport, the uptake of uracil being specifically decreased by GTP deprivation and that of adenine and guanine specifically decreased under conditions of stringent response (increase of ppGpp). Although GTP is not used for the synthesis of a cell wall precursor, its decrease caused a decrease in wall synthesis. As wall synthesis and cell septation, which is important for cell division as well as sporulation, seem to depend on the opening of crosslinks in the cell wall and may in turn be correlated with wall turnover, the latter, which can be easily quantitated, was studied. Wall turnover is usually assumed to depend on known autolytic enzymes. But it was found that different mutants, deficient in known autolytic enzymes, exhibited the same rate of turnover as the standard strain. Therefore, some unknown enzyme seems to control wall turnover and may be important for wall synthesis.

Interestingly, all conditions reducing the rate of cell expansion, including those causing sporulation, decreased the rate of turnover, as if turnover depends on the physical separation of mucopeptides from other molecules that inhibit their hydrolysis.

In addition to the massive sporulation resulting from GTP deprivation, certain mutations or amino acid analogs (e.g., ethionine) greatly increased the frequency at which cells continually switch from cell division to spore development. In some mutants this continual sporulation resulted from a slightly reduced activity of pyruvate carboxylase which, by reducing the concentration of aspartate, caused a slight stringent response throughout growth. Such results demonstrate that minor alterations in the function of an enzyme, which cannot be detected by changes in cellular growth properties, can have major repercussions for differentiation. Introduction of a relaxed (rel) mutation prevented the increased sporulation. Ethionine addition or secondary mutations resistant to ethionine produced a high frequency of continual sporulation even in rel strains. Because the resistant mutants contained only 2% of the normal S-adenosylmethionine synthetase, a partial deficiency of S-adenosylmethionine apparently causes an increase in the frequency at which cells continually enter sporulation. It is worth noting that a deficiency of DNA methylation has been shown to increase the frequency of differentiation in eukaryotic cells.

2. Cloning of the gene for glucose dehydrogenase. Although many proteins participate in development, for only a few of them is an enzymatic property known. Of particular interest is glucose dehydrogenase because this enzyme is synthesized exclusively in the forespore cell compartment, which is surrounded by two membranes having opposite polarity. As it is not known how the synthesis of any developmental enzyme is controlled, the Laboratory has made specific antibodies against glucose dehydrogenase and used them to isolate clones of DNA containing the gene for glucose dehydrogenase. Surprisingly, the gene, which is not expressed in growing B. subtilis cells, produced highly active glucose dehydrogenase in Escherichia coli. By using a plasmid which did not contain any promoter in the neighborhood of the single EcoRI restriction site into which the glucose dehydrogenase fragment was inserted, it was further shown that the isolated DNA fragment of B. subtilis contained its own promoter. This will now make it possible to determine whether the expression of this gene in vegetative B. subtilis cells is prevented by a specific repressor, whether a unique promoter enables transcription only by a changed RNA polymerase (e.g., production of a new sigma factor), or whether some other mechanism, e.g., at the translational level, is involved. Studies determining the genetic location of the gene and the role of this enzyme in sporulation or germination are also under way.

3. Mechanisms controlling meiosis and yeast sporulation. The eukaryote Saccharomyces cerevisiae is known to undergo meiosis before the four haploid nuclei develop into spores. Because 10^8 cells per ml enter this differentiation process almost synchronously, yeast provides an ideal system to study meiosis and its abnormalities which in humans lead to defects (e.g., Down's Syndrome). Whereas it was previously thought that yeast would enter meiosis and sporulation only under conditions of nitrogen starvation and the presence of acetate, the Laboratory has shown that partial deprivation of carbon, nitrogen, phosphate, or sulfur can initiate the process. To narrow

down further the suppressor compound, inhibitors and mutants were used. Although most inhibitors cannot enter the highly protected yeast wall, hadacidin, an aspartate analog and ribovirin, an inhibitor of GMP synthesis, inhibited growth and induced sporulation. Also in mutants deficient in the synthesis of guanine and uracil nucleotides sporulation usually occurred when either of these nucleotides was partially deficient. Analysis of nucleotide pools by high pressure chromatography showed that the concentration of GTP or UTP, respectively, decreased when the corresponding base was missing. A further analysis of the sulfur-containing S-adenosylmethionine will be necessary before firm conclusions about the molecule controlling meiosis can be drawn. Because a detailed analysis of numerous HPLC peaks was needed, a system was developed to measure the whole spectrum of each eluate every 2.5 seconds, to store the information in a computer, and to determine the absorption maximum of each compound. This provided a novel way to identify compounds eluting from a column.

4. Characterization of developmental proteins. During the sequential development from a growing differentiated cell or from a fertilized egg into a whole organism, many developmental proteins are sequentially synthesized, and some of them are later destroyed again. The two-dimensional electrophoresis of proteins combined with radioautography or silver staining, makes it possible to follow the appearance and disappearance of all but minor proteins. To identify specific proteins appearing during development, ^{14}C-methylated or ^{32}P-phosphorylated proteins, enzymes to which iodinated antibodies bind, and proteins made radioactive by photoactivated covalent linkage of a radioactive ligand were identified. In addition, proteins with high affinity to GTP were isolated by affinity chromatography and then separated by two-dimensional electrophoresis. Numerous differences between normal cells and sporulation mutants were observed in B. subtilis. The same technique was also used for individual mouse embryos making it possible to identify the time of development at which certain proteins appear. Individual enzymes and receptor proteins are now being identified.

5. Control of the synthesis of neuro-receptor proteins. Earlier experiments performed in this Laboratory using HeLa cell lines had shown that short-chain fatty acids, in particular butyrate, caused an increase in the number/cell of beta-adrenergic receptors and of the proteins coupling them to AMP-cyclase. It has now been shown that these receptor proteins and the proteins coupling them to the cyclase also increase greatly when cells are transferred from a serum-containing medium to one containing basal nutrients and certain hormones. This phenomenon results in part from the absence of catecholamines and in part from the presence of epidermal growth factor. When the HeLa (ES-1) cells were grown in the basal medium supplemented only with epidermal growth factor and hydrocortisone but no insulin, many beta-adrenergic receptors were produced but they were not coupled to adenylate cyclase. Thus insulin is essential for this coupling. Further experiments investigated whether the increase in receptor proteins resulted from an increase in receptor synthesis or a decrease in degradation. For example, tunicamycin, an inhibitor of protein glycosylation, caused an increase in the number of receptor proteins per cell because it prevented their degradation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02365-04 LMB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Intercellular Communications and Transmembrane Signals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. C. Henneberry	Chief, MNS	LMB NINCDS
OTHERS:	P. Lysko	Senior Staff Fellow	LMB NINCDS
	R. Elliott	Visiting Fellow	LMB NINCDS

COOPERATING UNITS (if any)

Developmental and Metabolic Neurology Branch, NINCDS

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Molecular Neurobiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major goal of this project is to understand the biochemical events involved in the response of individual cells to external signals. We have previously shown that several types of hormone/neurotransmitter receptors increase in several cell lines when the cells are grown in the presence of certain short-chain fatty acids. This ability to modulate receptor expression has permitted us to analyze the biochemical events in adenylate cyclase activation by extracellular signals. In FY 82 we have concentrated on adapting several human cell lines to growth in serum-free media and examined the effects on receptor number and function. Our aim is to study the interactions of several hormones acting simultaneously on the same cell under well-defined conditions not possible with serum present. Elimination of serum causes a striking increase in beta-adrenergic receptor number partly explainable by release from down-regulation due to catecholamines in serum; however, we have also found important roles for other media components in the regulation of receptor number and function.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01886-12 LMB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Control of Meiosis and Morphogenesis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. B. Freese	Biologist	LMB NINCDS
OTHERS:	Z. Olempska-Beer	Visiting Associate	LMB NINCDS
	A. Hartig	Visiting Fellow	LMB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Developmental Biology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Meiosis and sporulation of the yeast Saccharomyces cerevisiae can be initiated by partial deprivation of carbon, nitrogen, phosphorus, or sulphur sources. It can also be induced by the deprivation of guanine or, less efficiently, uracil nucleotides. It can be prevented by the addition of methionine plus adenine or by S-adenosyl-methionine (SAM). The results suggest that meiosis may be controlled by some methylation reaction.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02527-01 LMB

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Role of Methylation and Differentiation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Freese	Chief	LMB NINCDS
OTHERS:	K. Ochi	Visiting Associate	LMB NINCDS
	H. Nakashita	Visiting Fellow	LMB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Developmental Biology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sporulation of B. subtilis could be induced by the stringent response to partial amino acid deprivation; relaxed (rel) mutants could not be induced. The induction was prevented by certain antibiotics when they were added at concentrations at which they had almost no effect on growth. Mutants (spd) were isolated which sporulated continually in a medium (with excess glucose) in which normal B. subtilis strains do not sporulate. Some of them were partially deficient in amino acid synthesis, and the introduction of a (rel) mutation prevented this effect. Other spd mutants sporulated continually when in a rel background; they had 50% less than the normal S-adenosyl-methionine (SAM) synthetase activity. Addition of partially inhibitory concentrations of ethionine or seleno-methionine to a rel mutant induced sporulation, and ethionine resistant mutants deficient in SAM synthetase sporulated during growth at increased frequency. Apparently, reduced methylation of some cell component increases the frequency of spontaneous sporulation.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01244-18 LMB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Control Mechanisms and Differentiation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Freese	Chief	LMB NINCDS
OTHERS:	H. Cheung	Visiting Fellow	LMB NINCDS
	B. Uratani	Visiting Associate	LMB NINCDS
	N. Vasantha	Visiting Associate	LMB NINCDS
	L. Vitkovic	Senior Staff Fellow	LMB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Developmental Biology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5.5	4.0	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Various parameters related to the onset of bacterial differentiation (sporulation) were investigated. It was found that guanine nucleotide deprivation, responsible for the initiation of sporulation, caused a drastic decrease in the synthesis of rRNA and tRNA but only a small decrease in the synthesis of mRNA. Cell wall synthesis and cell wall turnover were also reduced. The latter decreased under any conditions decreasing the expansion of the cell. The decrease of GTP also caused a decrease in uracil uptake, whereas the stringent response (increase of ppGpp) to amino acid deprivation caused a decrease of purine uptake. The gene of glucose dehydrogenase, and enzyme made only in the forespore compartment, was isolated by cloning in lambda charon phage. The insertion piece also contained a promoter that allowed production of high amounts of glucose dehydrogenase in E. coli. A bypass of fructose bisphosphatase was discovered and mutants (gene symbol bfd) deficient in it were isolated. Strains can grow on gluconeogenic carbon sources if either the fdp or the bfd gene is functional.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02364-04 LMB

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development and Teratology in Rodent Embryo Culture

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. C. Henneberry	Chief, MNS	LMB NINCDS
OTHERS:	A. Bruckner	NIH Expert	LMB NINCDS
	P. Grojec	Visiting Fellow	LMB NINCDS

COOPERATING UNITS (if any)

Office of Biometry and Field Studies, NINCDS

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Developmental Biology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.8	2.3	0.5

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major goals of this project are (1) to adapt newly developed methods of embryo culture for teratogenicity studies; (2) to determine the teratogenic potential of certain lipophilic drugs selected on the basis of their strong growth inhibition of cultured mammalian cells; and (3) to evaluate the utility of the embryo culture system for basic studies in developmental biology. In FY 82 we completed a study showing that the anticonvulsants valproic acid and diphenylhydantoin cause developmental defects in a dose-dependent manner, independent of maternal metabolism. We also adapted two-dimensional electrophoretic techniques and improved silver-staining methods for computer-assisted analysis of embryo proteins. The proteins from a single 10-day mouse embryo can be analyzed by this approach, permitting studies on the appearance of certain identifiable proteins during early stages of development.

PHS-6040
(Rev. 2-81)

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Molecular Genetics
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Molecular Genetics
National Institute of Neurological and Communicative
Disorders and Stroke

Robert A. Lazzarini, Chief

The Laboratory of Molecular Genetics was officially established on January 30, 1981. Thus far, the major efforts of the Laboratory have been administrative, largely directed toward recruiting personnel, acquiring designated space, and ordering equipment. During its first year, however, the Laboratory has had a quantum growth jump: the section on Electron Microscopy, IDB, NINCDS was transferred to the Laboratory of Molecular Genetics and established as a new section. Consequently, the Laboratory now has three sections: the Molecular Virology Section, the Recombinant Genetics Section, and the Neural and Molecular Ultrastructure Section (formerly the section on Electron Microscopy, IDB).

The research programs of all three sections have been integrated, and a number of new program initiatives are now under way. Substantial advances have been made in each of the sections' programs. Summarized below are the advances made in the Recombinant Genetics Section and the Molecular Virology Section. The activities of the Neural and Molecular Ultrastructure Section will be reported this year as part of the IDB Annual Report.

The Recombinant Genetics Section has defined its first major research program: the study of myelin formation and its regulation. This is an umbrella program that covers both the molecular and cellular aspects of the developmental program which culminates in myelin sheath formation. The Recombinant Genetics Section will contribute principally the molecular studies, while the Neural and Molecular Ultrastructure Section will contribute studies at the cellular level. Four proteins of a peripheral and central nervous system have been targeted for initial study--the myelin basic protein, P_2, P_0 and proteolipid. The first phase of the molecular level studies is the cloning of the genes coding for these proteins. To this end, we have obtained the necessary human perinatal brain tissue, prepared cDNA libraries from brain mRNA's, and we are presently searching among the five hundred library clones to identify those which contain the genes for myelin basic protein. We have tentatively identified several such clones and are characterizing them extensively to establish whether they contain the desired genes.

The Molecular Virology Section has successfully assembled a clone for the vesicular stomatitis virus gene coding for the nucleocapsid protein. This clone has been shown to be functional when appropriately positioned in expression vectors. Using an SV40 vector, we have obtained quantities of a protein whose synthesis is directed by the recombinant gene. This protein appears in every way to be identical to that formed during a virus infection. We have also obtained expression of the cloned gene in the prokaryotic cell, E. coli. Currently, this protein produced by the recombinant gene is being employed in studies of viral assembly--the formation of a viral nucleocapsid structure from purely recombinant genetic elements. If successful, these studies will open the way to the production of hybrid viruses which will have numerous clinical, as well as basic applications.

The Molecular Virology Section has also employed recombinant DNA techniques to study the structure of viral chromosomes. By preparing DNA copies of RNA virus chromosomes, we have been able to study the structure (sequence) of the viral nucleic acid. During the last year, we have employed these techniques to establish that a defective interfering particle of VSV is a "Simple Deletion" mutant and to precisely establish the sequences around the deletion point. These sequences were crucial in ruling out certain models for the formation of DI particles and for establishing the reasonableness of a generalized model proposed by us.

CONTRACT NARRATIVE
Laboratory of Molecular Genetics
Fiscal Year 1982

UNIVERSITY OF VIRGINIA (NOI-NS-12353)

Title: Large Scale Preparation of VSV DI Particles, and E. coli Plasmid DNA Containing VSV Sequences.

Contractor's Project Director: Dr. Jay C. Brown

Current Annual Level: $81,900

Objectives: To establish conditions for the growth and purification of VSV defective particles which will reproducibly yield materials of the requisite purity and activity, to devise procedures for the purification of plasmid DNA's that contain VSV sequences, and to supply such materials to the Laboratory of Molecular Genetics, IRP/NINCDS.

Major Findings:

a) Conditions and procedures have been devised for the purification of the virus particles and plasmids. Materials prepared by this new scheme meet the specifications set forth in the contract.

b) The contractor has delivered to the Laboratory of Molecular Genetics, IRP/NINCDS, the amounts of purified VSV DI particles and plasmid DNA stipulated in the contract.

c) The contractor has established procedures for the preparation of plasmid DNA from E. coli and has supplied the materials designated on the contract.

Significance to the NINCDS Program and Biomedical Research: The procedures and materials developed under this contract are immediately used by the Molecular Genetics Laboratory. This contract, therefore, forms an integral part of the Laboratory's research program, namely, the regulation of viral nucleic acid synthesis in animal cells. This contract has supplied the Program with the raw materials for RNA sequencing of the viral genomes. These studies have characterized sites on the chromosomes that are important for autointerference, DI particle genesis, and the replication of the viral genome.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02026-10 LMG

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Viral Nucleic Acid Synthesis in Animal Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. A. Lazzarini	Chief, Lab. of Molecular Genetics	LMG	NINCDS
OTHER:	M. Schubert	Staff Fellow	LMG	NINCDS
	J. Condra	Staff Fellow	LMG	NINCDS
	Y. Murooka	Visiting Scientist	LMG	NINCDS
	F. Yang	Visiting Fellow	LMG	NINCDS
	B. Gitomer	Visiting Fellow	LMG	NINCDS
	S. Yamaguchi	Psychologist	LMG	NINCDS
	J. Sprague	Chemist	LMG	NINCDS
	H. Arnheiter	Guest Worker	LMG	NINCDS
	G. Harmison	Chemist	LMG	NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION
Molecular Virology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7.5	6.0	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long range objective of this project is the description of the component molecular events involved in the replication of the negative strand viruses (myxo, paramyxo, rhabdo, arena and bunya viruses). The topics that are currently being investigated are:

1. The origin of DI particles.
2. Nucleocapsid assembly.

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(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02528-01 LMG

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Myelin Synthesis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. A. Lazzarini	Chief, Lab. of Molecular Genetics	LMG	NINCDS
OTHER:	N. Zeller	Staff Fellow	LMG	NINCDS
	H. Arnheiter	Guest Worker	LMG	NINCDS
	S. Yamaguchi	Psychologist	LMG	NINCDS
	J. Sprague	Chemist	LMG	NINCDS

COOPERATING UNITS (if any)

Department of Biology, University of Maryland

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION
Recombinant Genetics Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Four proteins of a peripheral and central nervous system have been targeted for study--the myelin basic protein, P_2, P_0 and proteolipid. The first phase of the molecular level studies is the cloning of the genes coding for these proteins. To this end, we have obtained the necessary human perinatal brain tissue, prepared cDNA libraries from brain mRNA's, and we are presently searching among the five hundred library clones in order to identify those which contain the genes for myelin basic protein. We have tentatively identified several such clones and are characterizing them extensively to establish whether they contain the desired genes.

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(Rev. 2-81)

TAB 12 -- LABORATORY OF NEURAL CONTROL -- LNLC/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Neural Control, Intramural Research Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Neural Control, Intramural Research Program
National Institute of Neurological and Communicative Disorders and Stroke

Robert E. Burke, M.D., Chief

Introduction

Research work in the Laboratory of Neural Control (LNLC) is devoted largely to studies of the central and peripheral neural mechanisms involved in the control of movement in mammals, emphasizing neural organizations at the level of the spinal cord and those regions of the brain stem and cerebral cortex that project directly to the spinal cord.

Present Organization

During FY 1982, the staff of the Laboratory of Neural Control (LNLC) has consisted of up to 10 investigators (four permanent senior scientists and six post-doctoral fellows). The permanent staff also includes three senior support personnel (two engineers and one physiologist), a biological technician, and the laboratory secretary. Non-permanent, part-time staff includes one Laboratory Aide and a student computer programmer. Because of the close interaction and collaboration among the Laboratory staff, LNLC has not been divided into formal Sections. The research effort can be described under four general headings, divided roughly by methodological approach:

1. Electrophysiological and morphological analysis of the cellular physiology and neuronal circuitry operating in the control of movement at the spinal cord level, largely using acute, reduced preparations (both cats and monkeys).
2. Projects that utilize novel methods for recording the activity of individual neural elements, activity patterns in whole muscles, and kinesiological data in awake, intact animals (both cat and monkey) that are comfortable and performing normal motor behaviors.
3. Theoretical and computer modeling studies of information processing in neural networks, or of the properties of complex elements such as muscle spindles.
4. Activities concerned directly with the development of new instruments and techniques, and the further refinement of existing methods, for recording and analyzing neurally-relevant data from intact, freely moving animals.

Project Summaries:

Systematic study of the output elements of the motor system, the motor units, is included in a project entitled "Intrinsic Properties of Motor Units". This continued in FY 1982 primarily with studies of the detailed morphology of type-identified α-motoneurons, labeled by intracellular injection of horseradish peroxidase (HRP). This involves reconstruction of entire motoneurons from serial sections, with measurement of the legnths, diameters, and branching patterns of their dendrites. Initial evidence provides for the first time direct evidence that the membrane area of α-motoneurons varies with motor unit type: FF motoneurons statistically have the largest total areas, type S the smallest, and type FR are intermediate in size. Preliminary data also suggests

that the specific membrane resistivity of type S motoneurons is likely to be two- to three-fold greater than that of type FR or FF cells. These findings have important implications for resolution of controversies about the mechanisms by which motor unit recruitment is controlled. We are currently comparing detailed reconstructions of motoneurons with data about their electrophysiological input resistance, membrane time constant, and dendritic electrotonic length. Using the anatomical data, we can then construct realistic computer compartmental models to constrain possible ranges of variation in specific membrane properties in different cell types.

Work on the "Motor Control Systems in the Spinal Cord" is closely related to the above and includes several aspects. The first has been a continuation of studies, begun about 5 years ago, of the detailed anatomy of the intraspinal trajectory of group Ia muscle stretch receptor (group Ia) afferents, and of the contacts they establish on defined types of α-motoneurons. This work depends on intracellular injection of HRP into functionally identified afferents and, subsequently, into type-identified motoneurons. Over 20 functionally identified afferent-motoneuron pairs ("contact systems") have now been fully reconstructed at the light microscope level. These show synaptic boutons arranged in a variety of configurations, from quite localized to very dispersed. Measurements of the postsynaptic motoneuron dendrites have permitted estimation of the electrotonic distance between individual boutons in a given system and the motoneuron soma. Depending on the choice of postsynaptic membrane characteristics, boutons from a single Ia afferent to a given motoneuron may occur at any electrotonic distance, up to maximum values (2 - 4 length constants), and the contacts can be dispersed over 1 to 1.5 length constants. Such electrotonic dispersion appears to be the rule rather than the exception. This finding represents a considerable departure from expectations based on earlier electrophysiological evidence from this and other laboratories around the world. The number of boutons in a given contact system is variable, ranging from 4 to 35 for homonymous systems (i.e., afferents that project to motoneurons of the same muscle), and 3 to 6 for heteronymous (synergist) contact systems.

A related subproject concerns the interaction of post-tetanic potentiation (PTP) with primary afferent depolarization (PAD) in group Ia afferents in the cat spinal cord. PTP is produced by prolonged, high frequency tetanization of the Ia afferents in a muscle nerve (e.g., medial gastrocnemius), while PAD is generated by short volleys delivered to group I afferents in certain other muscle nerves, such as those from the hamstring muscles. PTP and PAD are the two main mechanisms by which synaptic transmission can be modulated presynaptically, but there has been surprisingly little study of their interaction. We have found that tetanization of a group of Ia afferents markedly increases PAD, as measured by micropipette recordings within individual group Ia afferent axons, and by measures of afferent excitability to direct electrical stimulation within the ventral spinal gray matter. At the same time, presynaptic inhibition of group Ia excitatory postsynaptic potentials (EPSPs) is markedly enhanced in the wake of a conditioning tetanus to the Ia afferents. The evidence available from these experiments is necessarily indirect but it is consistent with the view that PAD is generated by a postsynaptic conductance change in afferent terminal arborizations produced by axo-axonic synapses. However, the shape of phasic PAD potentials recorded intra-axonally, and the time course of changes in PAD shape after a conditioning tetanus to Ia fibers, suggest that the presynaptic transmitter produces complex changes in the membrane conductance of group Ia synaptic terminals which cannot be entirely accounted for with conventional models.

A final aspect of this project has been continued investigation of the organization of synaptic input systems that project to motoneurons of the flexor digitorum longus (FDL) and flexor hallucis longus (FHL) muscles. As reported previously, these anatomical synergists actually exhibit quite disparate functional activity patterns in intact cats. Intracellular recording and electrical stimulation of a wide variety of peripheral nerves suggest that some polysynaptic systems can make quite different patterns of connection with FDL and FHL motoneurons but the differences in these peripheral inputs seem insufficient to account for the marked functional disparity. Therefore, we have examined the behavior of FDL and FHL motor pools during fictive locomotion in decerebrate cats that are paralyzed and immobile. In this preparation, all phasic sensory input is abolished but the functional activity patterns of FDL and FHL are exactly the same as found in the intact cat. Thus, the functional disparity between these motor pools must result from highly specific synaptic inputs from the "central locomotor pattern generator" that is known to exist in the spinal segments, and which can operate to produce locomotor rhythms without any phasic sensory feedback. This observation opens the way for a continued exploration for interneuronal systems that must separately drive the two motor pools, which will continue in FY 1983.

The project entitled "Neuron Activity in Locomotion" is designed to test ideas about motor control that derive from more conventional, neurologically reduced preparations. The work has depended on the development of new methods and techniques that permit recording the activity of individual neural elements in freely moving cats, along with the force and length of individual muscles or muscle groups, and the movements of the entire animal. Chronically implanted electrodes and transducer devices have been developed to permit recording temporally correlated, multi-channel data streams. The systems available in LNLC at present permit relatively reliable chronic recording from individual, functionally-identified sensory afferent neurons and α-motoneuron axons, as well as mass activity from peripheral nerves and muscles, in freely-moving, intact cats during normal motor behaviors.

During FY 1982, considerable progress was made in elucidating the action of γ-motoneurons in modulating muscle spindle stretch receptor sensitivity during normal movement. A key development was a new nerve cuff electrode combined with a microcatheter, through which dilute solutions of local anesthetic can be injected. The anesthetic, in proper doses, can produce relatively selective blockade of the fine γ-motor axons, leading to functional spindle de-efferentation during the course of a movement behavior like locomotion and permitting inferences about fusimotor control in the intact animal. This work has revealed clear evidence of bursts of γ-motoneuron action that are phased with the step cycle. It is also possible to compare the movement behavior of individual spindles with their responses to standardized tests in the anesthetized animal. The results have led to data which will serve as the basis for a computer model of spindle behavior (see below) that is fully testable in the intact animal - something that has never before been possible.

Chronic microelectrode implant methods also permit recording the firing patterns of individual α-motoneuron axons in the spinal ventral roots during normal motor behaviors. The bursts observed during normal locomotion exhibit few "doublets", in contrast to observations in decerebrate or fictive stepping. Moreover, motoneurons show a much wider range of firing frequency modulation than anticipated on the basis of previous indirect evidence. The frequency envelope of burst firing by single motoneurons recorded during normal stepping shows, in many cases, a close similarity to the whole muscle EMG. Such cases

suggest that the EMG signal can be used to represent the excitatory driving function to the motoneuron pool. This notion has been tested experimentally by injecting rectified and filtered versions of EMG records into motoneurons via intracellular pipettes, which produces firing patterns very similar to those observed for units recorded during the same step cycles.

The representation of motor pool drive by the EMG signal is, however, tempered by our recent observations that some muscles with complex morphology may in fact contain more than one functional pool of motor units. The sartorius muscle of the cat, for example, gives evidence of containing at least two, and very likely three, distinct populations of motor units, each of which is active in only one phase of the step cycle. The whole muscle EMG exhibits multiple bursts but each of these bursts is apparently composed of different sets of motor units. This surprising finding represents a variation on the theme already described with the FDL-FHL muscle pair - i.e., groups of motor units arranged in parallel (in this case, within the same muscle) but performing different functions. These observations suggest that the CNS must deal with the control of populations of motor units comprising "task groups" which are not necessarily organized according to muscle anatomy. Thus, it appears likely that the notions of "synergists", antagonists", and even of "muscles" as discrete entities, that have been developed on the basis of gross anatomy may well not always reflect the actual patterns of functional organization.

Over the past year or two, the above project has become more and more closely linked with that devoted to "Models of Neural Interactions". Much of the current work in the latter project is devoted to development of strategies and methods for handling the multichannel data streams that emerge from chronic recording experiments. This effort has taken two forms, one primarily concerned with data reduction techniques, and the other with the development of computer-based models that emerge from experimental data but which serve as conceptual frameworks for understanding and describing experimental results, rather than as data reduction tools. Considerable progress has been made in the development of computer programs to permit reduction and display of complex data from locomotion experiments, particularly in applications in which stimulus timing must be integrated with phase information about step cycles that are nearly, but not exactly, equal in duration.

With respect to the development of conceptual models, several aspects deserve mention. First, experimental data about the behavior of muscle spindle stretch receptors studied in intact cats, with and without γ-motoneuron drive (described above), have permitted formulation of a computer model of spindle function that results in predictions that can be tested in intact animals. The behavior of a given muscle spindle, already recorded during normal movements, can be tested with controlled limb manipulations with a torque motor device under deep anesthesia (to eliminate fusimotor effects) to permit quantitative inferences to be made about fusimotor effects. Second, the wealth of experimental data already at hand about the length and force trajectories of a variety of cat hindlimb muscles (reported in previous Annual Reports), plus the growing evidence for the existence of "task-groups" of motor unit pools (see above), has stimulated the initial development of a computer model of the cat hindlimb, which will include a framework based on the static anatomy of the bones, joints, muscles, and moments of inertia of the hindlimb. Upon this we can superimpose dynamic conditions of movement, constrained by experimental data about joint angles, limb trajectories, limb loading, and the activities of individual muscles as signalled by EMG recordings and implanted tendon force transducers. Such a model will be of enormous potential utility in defining

members of task-groups, in understanding their patterns of activity during stereotyped and non-stereotyped movements, and in making sense of the complex activity patterns observed for stretch and force receptor afferents that emerge from task-group members. Finally, a collaborative project with the University of California, San Francisco, on a new model of auditory signal processing and pitch perception was completed in FY 1982. This model suggests that recognition of mid-range frequencies may be accomplished by precise timing comparisons made by neurons in the medial superior olivary nucleus.

Work on "Cortical Mechanisms of Voluntary Motor Control" has, during FY 1982, continued to concentrate on activity patterns, recorded during voluntary movement in awake monkeys, of neurons in regions of the arm and hand area of the cerebral cortex that have relatively direct pathways to the spinal cord and brain stem (the sensorimotor cortex and supplementary motor area). Of particular interest is the influence of sensory input in modulating cortical cell activity. Current studies have focussed on the effect of brief passive shortening of tonically active muscles. Such perturbations most often result in silencing cortical units that are tonically active during maintained contraction of the shortened muscle, a result that is consistent with the currently controversial notion of "long-loop" cortical reflexes. LNLC has recently received several monkeys with unilateral or bilateral forelimb deafferentation. These animals are being trained to perform arm and hand tasks similar to those used with intact monkeys. Although it is more difficult for deafferented animals to learn the precise movements necessary, preliminary indications suggest that they will acquire the requisite facility. When the animals are fully trained, the behavior of cortical units will be tested and compared with results from comparable samples of units from normal animals, in order to infer the role of sensory information in the control of cortical cell action. Definition of "comparable samples" is a difficult problem in such research but will include criteria such as anatomical location, presence or absence of pyramidal tract axons, location in regions in which intracortical microstimulation produces localized muscle activation, and definition of monosynaptic projection to particular muscles by spike-triggered averaging, all of which have been used in the normal monkeys.

A subproject of considerable interest is built on evidence reported previously that the flexor carpi ulnaris (FCU) muscle of the monkey forearm has a complex internal architecture with very different muscle fiber populations on either side of the central tendon. Studies are underway of the possibility that the two halves of FCU represent another example of two motor unit task-groups that have different functions but reside within a single muscle. Attempts to determine whether the two halves of FCU are innervated by anatomically distinct populations of motoneurons (i.e., spinal cord motor nuclei) have led to investigation of novel double-labeling methods using retrograde transport of exogeneous substances, primarily combining horseradish peroxidase and wheat germ agglutinin.

Work done under the project entitled "Techniques for Making Contact with the Nervous System" largely results from requirements generated by other projects in LNLC, although some input is received from outside groups in terms of questions or specific fabrication needs. A number of new observations described above directly result from these efforts (e.g., the combined catheter - nerve electrode cuff for chronic implantation). Evaluation of a miniature Ta-Ta_2O_5 capacitor stimulating electrode, suitable for chronic implantation in the cortex or in deeper structures, has continued during FY 1982, in collaboration with members of the Neural Prosthesis Program of NINCDS. This electrode design,

first developed some years ago in LNLC, has theoretical advantages for neural prosthesis applications and it has undergone substantial improvement in terms of miniaturization, due to technical advances in fabrication. During FY 1982, additional developments have included: 1.) a new treadmill system for the locomotion experiments, especially designed to minimize electrical and auditory interference and to improve speed and stability of belt movement; 2.) a behavioral training apparatus for cats designed to permit isometric force tasks for hind- or forelimb; 3.) improvements to the percutaneous connector and cable system that permits leadoff of up to 40 simultaneous data channels from freely moving cats; 4.) an interface system between the widely used Nicolet signal-averaging devices and the PDP series of laboratory computers; 5.) devices that facilitate anatomical reconstruction of neurons from serial microscope sections; and 6.) a series of modular electronic devices required for signal processing in several LNLC projects. All of these items are designed within LNLC and most are also fabricated in-house. The staff members involved also continue to consult with other laboratories within NIH and in other institutions around the world.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01686-14 LNLC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Motor Control Systems in the Spinal Cord

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Robert E. Burke, M.D.	Chief	LNLC NINCDS
Other:	James W. Fleshman, Ph.D.	Staff Fellow	LNLC NINCDS
	Loyd L. Glenn, Ph.D.	Guest Worker	LNLC NINCDS
	Aharon Lev Tov, Ph.D.	Visiting Fellow	LNLC NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to provide information on the mechanisms operating within reflex systems in the spinal cord, which include alpha motoneurons as the output link, as well as on the interconnections and interactions between reflex pathways and control systems descending to the spinal cord from supraspinal centers. Particular consideration is also given to correlations between synaptic organization, intrinsic neuronal properties, and dynamic behavior of the alpha motoneurons and the motor unit type, defined by the physiological characteristics of the innervated muscle fibers.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01687-14 LNLC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Techniques for Making Connections with the Nervous and Musculoskeletal Systems

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Martin J. Bak	Electronics Engineer	LNLC NINCDS
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	Joaquin A. Hoffer, Ph.D.	Senior Staff Fellow	LNLC NINCDS
	Gerald E. Loeb, M.D.	Medical Officer (Res.)	LNLC NINCDS
	William B. Marks, Ph.D.	Research Physiologist	LNLC NINCDS
	Edward M. Schmidt, Ph.D.	Research Physiologist	LNLC NINCDS

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.4	1.1

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is intended to develop techniques for the acquisition and processing of neuroelectric signals from the central and peripheral nervous system in acute and chronic neurophysiological preparations. Because of this laboratory's continuing interest in sensorimotor neural activity during unrestrained movements, the project also includes development of chronically implantable mechanical transducers, catheters, and connectors.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01688-14 LNLC

PERIOD COVERED
October 1, 1981 to September 1982

TITLE OF PROJECT (80 characters or less)

Cortical Mechanisms of Voluntary Motor Control

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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	George M. Dold	Engineering Technician	LNLC NINCDS
	Lloyd Glenn, Ph.D.	Guest Worker	LNLC NINCDS
	Michael E. Gordon	Engineering Technician	LNLC NINCDS
	Frederick T. Hambrecht, M.D.	Head, Neuroprosthesis Program	FNP NINCDS
	Joan S. McIntosh	Physiologist	LNLC NINCDS

COOPERATING UNITS (if any)
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	0.9	1.6

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to investigate the size and spatial distribution of cortical "colonies" that are associated with individual muscles or closely related groups of muscles, as well as the activity of neurons in such colonies in the motor cortex during defined voluntary motor behaviors. Intracortical microstimulation (ICMS) is used to map regions that produce excitation or inhibition of particular muscles or muscle groups, and the resultant cortical maps are compared with these for synergist or antagonist muscle groups. Cortical cell discharge patterns during normal movements are evaluated with respect to the excitation or inhibition of muscle activity that is produced by ICMS. Intracortical capacitor stimulating electrodes are being evaluated for efficacy, stability and safety for chronic implantation.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02079-09 LNLC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Models of Neural Interactions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William B. Marks, Ph.D.	Research Physiologist	LNLC NINCDS
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	Gerald E. Loeb, M.D.	Medical Officer (Research)	LNLC NINCDS
	Naotoshi Sugano, Ph.D.	Visiting Fellow	LNLC NINCDS

COOPERATING UNITS (if any)

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SECTION

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.9	1.8	0.1

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with the detection of patterns of simultaneous activity among groups of neurons and muscles, with describing these patterns mathematically, and with the underlying principles of neural organization that these patterns may exemplify.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02080-09 LNLC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Neuron Activity During Locomotion

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Gerald E. Loeb, M.D.	Medical Officer, Research	LNLC NINCDS
Others:	Martin J. Bak	Electronics Engineer	LNLC NINCDS
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	Joaquin A. Hoffer, Ph.D.	Senior Staff Fellow	LNLC NINCDS
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.6	2.0	1.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A variety of new techniques are being used to monitor the afferent and efferent neural activity in the spinal cord of intact cats during normal and perturbed locomotion. Flexible wire electrodes in the lumbar dorsal root ganglia (DRG) and ventral roots record stable, identifiable unit activity which is correlated with kinesiological data including, of muscle force, length, and EMG activity from chronically implanted gauges developed for this project. Neurons are characterized by conduction velocity, anatomical origin, and modality using spike-triggered averaging of EMG signals and neurograms obtained from specially designed nerve cuff electrodes implanted around peripheral nerves. The reflex effects of various electrical stimuli to motor and cutaneous nerves are systematically examined as they vary through the step cycle. The normal functional use of the various hindlimb muscles is being surveyed during a variety of normal behaviors in an attempt to correlate these patterns with their anatomical specializations regarding muscle fiber type, orientation, and proprioceptive feedback.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02160-08 LNLC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Intrinsic Properties of Motor Units

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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	John P. Miller, Ph.D.	Guest Worker	MRB NIADDK
	W. Rall, Ph.D.	Staff Scientist	MRB NIADDK

COOPERATING UNITS (if any)
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Mathematics Research Branch, NIADDK
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.7	2.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to provide information on the ranges and distributions of the electrophysiological and morphological characteristics of alpha motoneurons and of the interrelated mechanical, histochemical and morphological properties of the muscle fibers innervated by them (i.e., the muscle unit) in various hindlimb muscles in the cat. In some experiments, motor unit populations in normal animals are compared with those in animals after various conditioning treatments.

PHS-6040
(Rev. 2-81)

TAB 13 -- LABORATORY OF NEUROCHEMISTRY -- LNC/IRP

ANNUAL REPORT

October 1, 1981 to September 30, 1982

Laboratory of Neurochemistry

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Neurochemistry, Intramural Research
National Institute of Neurological and Communicative Disorders and Stroke
Janet V. Passonneau, Chief

The Laboratory of Neurochemistry is composed of four sections, the Section on Cellular Neurochemistry, the Section on Neurochemical Pharmacology, the Section on Enzymes, and the Section on Neuronal Development and Regeneration. These sections are engaged in a variety of projects which are related to the functions of the central nervous system.

Section on Cellular Neurochemistry

The Section on Cellular Neurochemistry has three projects currently in progress.

a. Metabolic Profiles in Normal and Diseased Retina.

The study of metabolites linked to the production and consumption of energy-rich stores in the retina is in progress. Variable periods of dark-adaptation, and exposure to high intensity (250 foot candles) or dim light (2.5 foot candles) have been used to evaluate the effects on metabolism. Of particular interest are changes in cyclic GMP concentrations in the individual layers of the retina, since the concentrations of this compound vary dramatically in light and dark, and among layers of the retina.

Studies are also in progress to ascertain whether high- or low- intensity light is required to effect responses of the cyclic nucleotide system. By using filters, light of selected wave lengths is being tested in an attempt to determine whether rod and/or cone pigments are involved in the transduction phenomenon.

A collaborative effort with the Eye Institute has been a study of granular dystrophy of the cornea. The disease is a dominant autosomal-linked lesion which results in opaque granular aggregates in the stroma and can lead to impairment of vision. These studies have identified a high molecular weight protein which is unique to the diseased cornea. Another protein which resembles normal keratin accumulates in abnormally high amounts in the pathological state.

b. Coordinate Effects of Amphetamine on Brain Energy Metabolism and Protein Synthesis.

The effects of amphetamine on the body temperature of mice has been shown to be dependent on the ambient temperature. At temperatures greater than 20°C, the body temperature of the test animal is elevated by the drug, while at ambient temperatures

below 15°C, the body temperature is decreased. At intermediate temperatures the response varies with individual animals. Amphetamine has been found to inhibit brain protein synthesis and also to decrease the concentration of brain energy reserves, including glycogen, and high energy phosphates.

A method of assessing in vivo brain protein synthesis by amino acid incorporation in vitro has been developed. Glycogen, glucose, phosphocreatine and adenine and guanine nucleotides are measured by emzymatic techniques.

It has been possible to evaluate the effecs of amphetamines on brain protein synthesis and metabolic events. During drug-induced hyperthermia, brain protein synthesis is markedly inhibited, and the inhibition is tightly correlated to the body temperature of the animal. The inhibitory effect is seen at 40°-41°C. Hyperthermia of a similar magnitude induced in mice by extreme elevation of ambient temperature has a comparable effect on brain protein synthesis.

The induction of hyperthermia by either amphetamine or elevated ambient temperatures, results in decreases in brain energy reserves. These changes, unlike protein synthesis, have proven to be not so closely coupled to the individual ody temperatures.

c. Metabolic Correlates of Neuronal Transmission in the Hippocampal Slice.

Studies have been made to evaluate the hippocampal slice preparation from guinea pig brain as a model for electrophysiological and metabolic occurrences in vivo. The thickness of the hippocampal slice and the preparative procedures have been studied in detail. The physiological state of the slice was evaluated by the analysis of energy metabolites, and of the evoked orthodromic response in the dentate gyrus.

Energy metabolites decrease from in vivo concentrations during slice preparation, but recover to a new steady-state level within an hour of incubation in the perfusion chamber. The concentration of the compounds studied (adenylates, phosphocreatine, cyclic nucleotides, and lactate) remain stable for at least eight hours. The thickness of the slice had little or no effect in metabolite profiles from 0.5 to 1 mm. Thicker slices appeared to be energetically depressed. The method of preparation in which temperature, oxygen, and glucose were varied prior to incubation appeared to have little effect on metabolic recovery. However, the evoked response was compromised if the preparative medium were devoid of oxygen and glucose.

The relationship of increased energy stores to synaptic transmission was evaluated. The concentration of phosphocreatine in the slices was increased by incubation with varying concentrations of creatine in the medium. In such slices,

synaptic transmission during anoxia was prolonged, compared to preparations without creatine.

Cyclocreatine in the incubation medium presumably increases cyclocreatine phosphate in the slices. After incubation with cyclocreaine, synaptic transmission was prolonged during anoxia but to a lesser degree than with creatine. The effect was diminished after longer periods of incubation (5 hours). In addition, incubation with cyclocreatine elicited seizures-like discharges in the hippocampal slice.

Section on Neurochemical Pharmacology

a. Ischemia

The search for a biochemical basis for the loss of brain function following an ischemic episode continues utilizing several in vivo as well as in vitro models of ischemia. Previous studies on the neurochemical events that occur during recirculation have shown that both cyclic nucleotide and energy metabolism are perturbed. In addition, the degree of abnormality increases with increasing periods of ischemia.

Of particular interest was the large postischemic rise in cyclic AMP. Previously, this pathophysiological response was duplicated in brain slices by the addition of oxygen and glucose to a medium devoid of the materials. Of the agents tested, only adenosine, norephinephrine, histamine and certain prostaglandins stimulated the accumulation of cyclic AMP in the gerbil brain. Attempts to block the postischemic rise in cyclic AMP with the appropriate antagonists to these agents were unsuccessful. Even the deprivation of the divalent cations, magnesium and calcium, had little effect on the response.

A recent observation that the CA 1 neurons of the hippocampus died 4 days after 5 min of bilateral ischemia provides a useful model for the neurochemist to investigate the selecive vulnerability of certain neurons. Certain metabolites have been measured in the CA 1 and CA 3 regions of the hippocampus and in the cerebral cortex from 1.5 to 96 hours after 5 min of bilateral ischemia. There were many delayed changes in the levels of glucose, glycogen, glutamate and GABA up to 2 days following 5 min of bilateral ischemia, but the alterations were uniform in all regions examined. The metabolite profile in the CA 1 regions at 4 days of recirculation was substantially different from both control values and those seen in the other two regions. This undoubtedly reflects the infiltration of glia into the CA 1 region. The depression of cyclic AMP and elevation of cyclic GMP at 6 hours of recirculation may indicate a critical period in the selective loss of the CA 1 neurons.

b. Motor neurons diseases.

Mice were infected with ADR virus and various metabolites were examined in the cerebellum, cerebral cortex and spinal cord of affected (paralyzed) and unaffected mice. While the changes were relatively minor in the cerebellum and cerebral cortex, there were marked differences in the spinal cord. When the differences in the cyclic nucleotides, glycogen, ATP and P-creatine were examined in 3 regions of the spinal cord, the changes were most dramatic in the anterior horn. To determine if these derangements result from the paralysis, these metabolites are currently being measured prior to the onset of paralysis.

c. Experimental seizures.

The relationship of the energy status of the tissue to neural function is being examined in the hippocampal slice. Various neurological disorders including seizures and ischemia deplete the tissue of its energy stores and thereby lead to a dysfunction of the nervous system. Utilizing compounds such as creatine and cyclocreatine which should increase the endogenous energy stores, the failure of synaptic transmission to an anoxic episode is substantially delayed.

Section on Neuronal Development and Regeneration

The Section on Neuronal Development and Regeneration is continuing its investigation of the various factors involved in the use of a nerve graft to aid in the repair of injured nerve tissue. Another area of research seeks to determine how neurons exert their trophic influence on end-organs.

A. Nerve Allograft Studies

It has long been recognized that transplantation antigens on the cells of a nerve allograft evoke an immune reaction from the host and that this response inhibits host nerve fiber growth through the graft especially if it is longer than 2 cm. Previous work in this section has shown that the immunosuppressive agent cyclosporin A (CyA) prevents allograft rejection with the result that host axons can now regenerate through 4-6 cm of nerve. Current studies with CyA indicate that host axons which regenerate through a long nerve allograft are functional in that they can reinnervate denervated muscles. It has also been found that the dose of CyA can be reduced from a potentially toxic dose of 15 mg/kg to 5 mg/kg. This should permit long-term studies with CyA since late side effects of the drug are as yet unknown. CyA also prevents the rejection of nerve allografts in sensitized recipients, but it is ineffective in preserving nerve xenografts (grafts between different species like guinea pig to rat). Muscle as well as neuronal allografts survive during CyA treatment, but when CyA is abruptly stopped rejection eventually ensues. It is anticipated that work with CyA will continue particularly along avenues which might reduce allograft

antigenicity and promote the induction of immunological tolerance.

B. Neurotrophic Studies

The observation that taste buds disappear after denervation and reappear (via the differentiation of ordinary lingual epithelial cells) after reinnervation is one of the best documented examples of trophic nerve function. Although it is known that the sensory neuron mediates the trophic effect on buds, it is not known whether it is the A or B type of neuron which is responsible for this action. Since capsaicin is neurotoxic to the B-type neurons after injection into newborn rats, the development of taste buds was followed after treatment with this agent. It was observed that after capsaicin treatment, many B-type sensory neurons disappeared from sensory ganglia but taste buds and their innervation developed normally. This finding shows that the A-type neurons are the ones responsible for inducing and maintaining the buds.

In another study, motor axons were made to reinnervate denervated tongue tissue in an attempt to find out why these axons fail to cause taste bud formation. It was observed that despite their presence in the connective tissue, no motor axons penetrated into the epithelium where the induction of buds must occur. Further studies are needed to determine what property of sensory neurons permit these, but not other types of axons, to enter and remain in gustatory epithelium.

Section on Enzyme Chemistry

I. General program

The overall objective of the section is to investigate enzymology of particular relevance to neural function. The principal area of study is the mechanism of active transport for sodium and potassium ions. Related projects are directed at elucidation of possible mechanisms for regulating sodium transport and studies of analogous systems for calcium ion transport. Each of these is discussed below.

II. Studies on the mechanism of the sodium transport system

A. Background

Nerve cells function to receive signals, to transmit signals between points in the nervous system, and to modify these signals in the process of transmitting them to other cells. All of these processes require energy derived from cell metabolism. The basic link between cell metabolism and these various neural processes is the concentration gradient of sodium ions across the outer cell membrane (plasma membrane). Both the electrical activity and the specific neurochemical transmission of signals

utilize this store of potential energy. The Na^+ gradient is generated by a process of Na^+ extrusion that uses metabolic energy.

The principal mode of sodium ion extrusion from animal cells is one driven by the free energy of hydrolysis of ATP. This process is mediated by a protein, Na,K-ATPase, which is an integral component of the outer membrane of virtually all animal cells. Work from this and other laboratories has established that metabolic energy is transferred to the membrane protein by its direct phosphorylation by ATP. This phosphorylation induces a series of structural changes in the ATPase protein and these changes constitute the process that extrudes sodium ions from the cell in exchange for potassium ions. Previous work from this laboratory has included the initial demonstation of the sodium-dependent phosphorylation of the Na,K-ATPase (Fahn, Albers and Knoval, 1963), demonstration of the conformational transformation of the Ka,K-ATPase consequent to its phosphorylation (Fahn, Albers and Koval, 1966), demonstration of the low-energy nature of the enzyme acylphosphate complexed with ouabain (Albers, Koval and Siegel, 1972), the simultaneous and independent existence of sodium and potassium ion binding sites on the Na,K-ATPase (Albers, Koval and Swann, 1975). More recently we have engaged in a series of studies of the presteady-state kinetics of the enzyme phosphorylation reactions (Froehlich et al, 1976, 1979, Hobbs et al, 1980 and in press). These studies have been concerned with confirming more directly the earlier evidence for conformation changes accompanying phosphorylation and ligand binding. Recent results have included elucidations of the mechanisms of inhibition of the Na,K-ATPase by the potent inhibitors, vanadate and oligomycin B.

B. Current studies

Recent transient kinetics studies in collaboration with Froehlich (NIA) have been designed to establish the sequence of binding of cations to the pump protein in the different phases of the pump cycle. Current experiments suggest the existence of a tightly bound Mg^{++} at one stage of the reaction. Other experiments indicate a step in which Na^+ and K^+ may simultaneously bind in confirmation of deductions from earlier steady-state experiments.

III. Studies on regulatory mechanisms for the sodium pump.

A. Background

Although the primary function of the sodium pump in neurons is undoubtedly that of generating the ionic gradients which produce the resting cell membrane potential and drive various Na^+ dependent transport systems for neurotransmitters and nutrients, several hypotheses have been advanced for more specialized functions of the sodium pump. With respect to neural function, an interesting hypothesis arises from the observation

that a membrane hyperpolarization resulting from pump activity can occur. This electrogenic sodium pumping is a natural consequence of the observed stoichiometry of 3 Na^+ ions moved outward to only 2 K^+ moved inward per pump cycle. It remains to be established whether this hyperpolarization is under the sort of regulatory control that would make it an important factor in such processes as synaptic excitability. Other hypotheses suggest that the stoichiometry of Na^+ pumping relative to ATP hydrolysis may be under some type of regulatory control, thus producing a pump of varying efficiency.

These various theories postulate the existence of ancillary regulatory process: endogenous regulatory substances, modification by protein phosphokinases, etc. There are, in fact, recent reports of the isolation of endogenous factors from brain with ouabain-like inhibitory activity. Papers continue to be published claiming significant modification of Na,K-ATPase activity by neurotransmitters.

It now seems well established that there are two variants of Na,K-ATPase in brain tissue, one of which appears to be specific to neurons. A report has recently appeared suggesting that the relative amounts of these two ATPase "isozymes" might be influenced by the catecholamine levels in brain.

B. Current studies

We have confirmed the existence of two forms of Na,K-ATPase in rat brain. We have been unsuccessful in obtaining evidence of an influence of catecholamine levels on the relative amounts of these forms. We plan to explore other possible physiological roles for these two forms in brain.

Because the isozymes are distinguished primarily on the basis of differential sensitivities to cardioactive steroid inhibition, we are engaged in a detailed study of the mechanism of this type of inhibition. This study has so far produced two important results. We have developed a rapid kinetic method for determining the relative amounts of the two enzymes in a given sample. Secondly, we have observed conditions in which the binding kinetics of cardioactive steroid inhibition are not first order with respect to the inhibitor concentration. We are extending these observations in the expectation of obtaining insights into the mechanism of inhibition. Our current hypothesis is tha there are two parallel pathways for cardioactive steroid binding with different binding affinities. We have evidence for the formation of an initial drug-enzyme complex that does not produce inhibition.

IV. Structural studies of the purified Na,K-ATPase.

A. Background

The Na,K-ATPase consists of two types of subunits, alpha and beta, that are thought to exist in 1:1 proportions although the absolute stoichiometry within cell membranes is unknown. Both subunits are of high molecular weight and, although some preliminary efforts at determining primary structure have been made in a few laboratories, progress in this direction is likely to be slow. Because these large protein structures exist in a lipid matrix, there are only a few successful instances of obtaining crystalline membrane proteins. Thus, the likelihood of obtaining detailed three-dimensional structural information about the sodium pump seems small at present. One laboratory has reported a method for obtaining two-dimensional arrays of purified Na,K-ATPase which may be useful for electron diffraction studies.

Because of the fundamental importance of this system and the number of basic questions about its function that could be answered by structural information, some alternative approach would be valuable. Complex proteins are considered to have evolved from simpler structures with conservation of structural domains that have analogous functions in different proteins. For example, nucleotide binding sites are known to have common structures in a variety of different dehydrogenases. One might envision approaching the structure of a complex protein by delineating each functional domain as a separate entity.

One difficulty with this approach is that much of the important structure is dependent upon precise folding and apposition of primary chains so that functionally competent structures may not be expected to survive procedures that fragment the protein, although occasional successes have occurred. For example, it has been possible to isolate a functionally competent ATPase fragment of the myosin molecule.

We have previously attempted to isolate a fragment of the Na,K-ATPase that might retain ionophoric activity with respect to sodium ions (Shamoo et al, 1973 and later). The limited success of this attempt led to analogous experimentation with the Ca-ATPase of muscle sarcoplasmic reticulum and in this case, a fragment with divalent cation-specific ionophoric activity could be isolated.

B. Current studies

From earlier work with antibodies to the individual subunits of Na,K-ATPase (Jean et al, 1974 and later), we were able to demonstrate an antibody that blocked binding of the specific Na,K-ATPase inhibitor, ouabain, to the enzyme. This observation suggests that antibodies may be useful in defining structural domains of large enzymes. We are now in the process of developing monoclonal antibodies to the Na,K-ATPase. This is presently an informal collaboration among several laboratories. Upon developing a series of monoclonal antibodies to different

sites on the same protein, we expect to use these as reagents to identify functional domains in the intact enzyme and to identify corresponding fragments in proteolytic digests. Thus, these antibodies will be useful both in defining function and in aligning fragments to associate structure and function. Definition of small fragments associated with particular functions should provide a more manageable alternative to the direct approach of correlating function with primary amino acid sequence of the whole protein.

So far, our role in this collaboration has been to supply purified enzyme for use as antigen and to assist in the development of suitable screening procedures.

Several Na,K-ATPase-positive clones have been detected among a series of hybridomas developed against rat brain synaptic membranes by A. de Blas (SUNY, Stony Brook).

V. Calcium metabolism in electric tissue.

A. Background

Calcium ions are known to be involved in important neural functions, in particular in the release of neurotransmitters. Intracellular levels of calcium are regulated primarily by an ATP-dependent pump analogous to the Na,K-ATPase and by a Na^{+}/Ca^{++} exchange mechanism. Most intracellular functions of calcium are thought to be mediated by a regulatory protein, calmodulin. Electrophorus electric organ is a cholinergically innervated tissue that provides an opportunity to study the mechanism of calcium regulation in excitable tissues. It is known to have a high concentration of calmodulin.

B. Current studies

A Ca^{++}-dependent ATPase found in Electrophorus electric organ membranes has been characterized. It is found to share several characteristics with other plasma membrane Ca^{++}-ATPases which are though to be Ca^{++} pumps. However, this enzyme activity is not stimulated by exogenous calmodulin.

Calmodulin from electric organ has been purified and its further characterization is underway.

These two projects will be terminated because of the departure of the responsible investigators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 00813-21 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Enzymological Aspects of Neural Functions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	R. Wayne Albers	Head, Sec. on Enzyme Chemistry	LNC, IRP, NINCDS
Other:	Ann S. Hobbs	Staff Fellow, Enzyme Chemistry	LNC, IRP, NINCDS

COOPERATING UNITS (if any)
Jeffrey P. Froehlich (NIA), Gerontology Research Center, Baltimore, MD

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Enzyme Chemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.1	1.9	1.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is an investigation into the mechanism and structure of the enzyme, Na,K-ATPase, that catalyzes the ATP-dependent extrusion of sodium ions from neurons and other cells. Studies are proceeding along the following lines: (a) measurements of the transient (pre-steady state) kinetics of the phosphorylation and dephosphorylation reactions of the Na,K-ATPase; (b) experiments designed to define the relation of structure to function of different domains of the Na,K-ATPase molecule; (c) steady-state kinetic and ligand-binding studies directed toward elucidation of the mechanism of energy transfer from ATP hydrolysis to the ionophoric process.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01586-15 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Trophic Function of Neurons

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: A.A. Zalewski, Head, Section on Neuronal Development and Regeneration — LNC NINCDS

Other: A.K. Gulati, Visiting Fellow — LNC NINCDS

COOPERATING UNITS (if any)
T.H. Oh, Department of Anatomy, University of Maryland

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Neuronal Development and Regeneration

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Sensory ganglia contain two populations of neurons which can be identified by their size, organelle content, degree of myelination, or histochemical profile. Since the chemical capsaicin (the hot ingredient of red peppers) is neurotoxic to one of the groups of sensory neurons when injected into newborn rats, we used this drug to determine which type of neuron is responsible for causing taste bud development. Capsaicin treatment destroyed many of the B-type sensory neurons, but this loss did not interfere with the temporal pattern of development, number, or degree of innervation of the buds. It can, therefore, be concluded that the A-type sensory cells are the gustotrophic neurons. In another study, denervated tongue tissue was reinnervated by hypoglossal motor fibers in order to help resolve why these axons cannot induce taste buds. Although regenerated motor fibers were observed in the connective tissue of the tongue, none of these axons penetrated the epithelium where the buds are normally found. Since axons must enter the epithelium to induce buds, this result suggests that certain sensory, but not motor, axons are endowed with some unique property which permits them to enter and remain within appropriate epithelium.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02006-10 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Metabolism in Glioma and Neuroblastoma Cell Lines

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Janet V. Passonneau	Chief, LNC	LNC	NINCDS
Other:	Craig J. Cummins	Staff Fellow	LNC	NINCDS
	W. David Lust	Head, Sec. Neurochem. Pharm.	LNC	NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Cellular Neurochemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02142-08 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cerebral Metabolism in Altered Metabolic States of the CNS

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. David Lust	Head, Sec. Neurochem. Pharm.	LNC	NINCDS
Other:	Janet V. Passonneau	Chief, LNC	LNC	NINCDS
	Hajime Arai	Visiting Fellow	LNC	NINCDS
	Alexander Wheaton	Biol. Lab. Tech. (Micro)	LNC	NINCDS
	Gretchen K. Feussner	Chemist	LNC	NINCDS
	Yukisama Yasumoto	Visiting Fellow	LNC	NINCDS

COOPERATING UNITS (if any)

Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Neurochemical Pharmacology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.7	1.4	.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being performed on the neurochemical aspects of selective vulnerability induced by short-term ischemia. The CA 1 neurons of the hippocampus have been shown to disappear by 96 hours after 5 minutes of bilateral ischemia in the gerbil brain. This observation provides a model for the examination of the neurochemical events which lead up to the selective loss of neurons. Metabolites were measured in the CA 1 and CA 3 of the hippocampus and in the cerebral cortex. Marked changes in the levels of glycogen, glucose, GABA and glutamate were evident between 1.5 and 48 hours of recirculation. However, these changes were essentially uniform in the 3 regions examined. By 96 hours of postischemia, the metabolite concentrations in the CA 1 regions were substantially different than the other two regions which could be attributed to the infiltration of glia. The only differences between the CA 1 region and the other 2 regions were an elevation of cyclic GMP and a depression of cyclic AMP which occurred at 6 hours of recirculation. The 6 hour period appears to be critical to the eventual loss of the CA 1 neurons.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02254-06 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
The Use of Neurological Grafts to Repair the Injured Peripheral or Central Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Andrew A. Zalewski, Head, Sec. on Neuronal Development and Regeneration — LNC — NINCDS

Other: Adarsh K. Gulati, Visiting Fellow — LNC — NINCDS

COOPERATING UNITS (if any)
W. K. Silvers, Department of Human Genetics, University of Pennsylvania

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Neuronal Development and Regeneration

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.6	1.8	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Nerve allografts (grafts between genetically different members of the same species) are rejected by normal rats but not by rats that have been treated with the immunosuppressive agent cyclosporin A (CyA). Further studies have shown that host axons can regenerate through allografts in CyA-treated hosts and that these axons will reinnervate denervated muscles. CyA also prevents the rejection of nerve allografts in allogeneically sensitized recipients, but the drug is ineffective in preserving xenografts (grafts between different species; e.g., guinea pig and rat). Immunosuppressive treatment with CyA had to be continuous because if therapy is stopped, rejection occurs even when only minor histoincompatibilities exist. Allogeneic muscle and neurons also survive during CyA treatment; in the case of muscle, it becomes reinnervated by host axons while transplanted neurons can regenerate their axons and induce taste buds in tongue tissue.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02256-06 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Metabolic Profiles in Normal and Diseased Retina

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Janet V. Passonneau	Chief, LNC & Chief, Cellular Neurochemistry	LNC, IRP, NINCDS
Other:	Elizabeth K. Barbehenn	Expert Consultant	LNC, IRP, NINCDS
	W. David Lust	Head, Section on Neurochemical Pharmacology	LNC, IRP, NINCDS
	Deirdre Noelker	Biologist, Cellular Neurochemistry	LNC, IRP, NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Cellular Neurochemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.4	1.4	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are continuing on retinal metabolism employing freeze-dried sections of frog retina. The concentrations of adenyl nucleotides (ATP, ADP, and AMP) and P-creatine were measured as a function of dark adaptation or light exposure using 2 sec or 2 min of bright light (approximately 250 ft candles) as well as 2 hrs of dim light (approximately 2.5 ft candles). For AMP, although each area sampled gave discrete tightly-bunched sets of numbers, levels even within one layer could vary up to 2.5 fold. This was not true for the other metabolites measured. A fluormetric assay for calmodulin was developed utilizing its ability to stimulate calmodulin-dependent phosphodiesterase. Sensitivity of the assay ranged from 0.5 to 5 mg. Additional work to further increase the sensitivity is planned. A project will begin to study the adenyl nucleotides, P-creatine, and cyclic nucleotide levels in retinal layers of Irish setter dogs. Levels in normal setters will be compared to levels in dogs with an inherited rod-cone dysplasia in order to gain some insight into the nature and course of this degeneration.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02455-02 LNC

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Metabolic Correlates of Neuronal Transmission in the Hippocampal Slice

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Janet V. Passonneau	Chief, LNC	LNC	NINCDS
Other:	Tim S. Whittingham	Staff Fellow	LNC	NINCDS
	W. David Lust	Head, Sec. Neurochem. Pharm.	LNC	NINCDS
	Alexander B. Wheaton	Biol. Lab. Tech. (Micro)	LNC	NINCDS
	Yukisama Yasumoto	Visiting Fellow	LNC	NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Cellular Neurochemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.1	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The relationship between cellular metabolite levels and neuronal transmission is being investigated in hippocampal preparations in vitro. The concentrations of the adenylates, phosphocreatine, creatine, lactate, and the cyclic nucleotides are evaluated for slices during in vitro incubations of up to 8 hr, and during transient periods of anoxia and ischemia. The magnitude of the evoked field potential is also recorded. The rate and degree of metabolic recovery following decapitation appear to be dependent on slice thickness, but not on the presence of glucose and oxygen during the initial preparation period. In addition, creatine and cyclocreatine are being tested for their dose and time-dependent effects on high energy phosphates and duration of transmission during anoxia. Added creatine results in the elevation of phosphocreatine concentrations, while cyclocreatine presumably causes an accumulation of cyclocreatine phosphate. ATP levels are unaffected by added creatine, and decreased by cyclocreatine. Both compounds prolong transmission when present in concentrations from 5 to 25 mM, though cyclocreatine also appears to act as a convulsant.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02257-06 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Neuropharmacology of Cerebral Metabolism

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	W. David Lust	Head, Section on Neurochemical Pharmacology	LNC,IRP,NINCDS
Other:	Janet V. Passonneau	Chief, LNC	LNC,IRP,NINCDS
	Alexander B. Wheaton	Biol. Lab. Tech. (Micro)	LNC,IRP,NINCDS
	Yukimasa Yasumoto	Visiting Fellow	LNC,IRP,NINCDS
	Tim Whittingham	Staff Fellow	LNC,IRP,NINCDS

COOPERATING UNITS (if any)

Pharmacology Laboratory, Epilepsy Branch, NDP, NINCDS (Bldg. 36)

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Neurochemical Pharmacology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	0.9	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being performed on the relationship of the energy status of the hippocampal slice to synaptic transmission in the region of the dentate gyrus. Creatine and the cyclic analog, cyclocreatine, were added to the incubation medium for various periods of time and the concentration of creatine phosphate and cyclocreatine phosphate were determined. The perforant pathway axons were stimulated and the activity recorded in the region of the dentate gyrus during an anoxic insult. In the creatine studies, the loss of signal was delayed during anoxia which was attributed to a significant increase in the levels of phosphocreatine. At both 5 and 25 mM cyclocreatine, there was evidence of seizure discharge under normoxic conditions. In spite of this, the cyclocreatine still prolonged neuronal function during the anoxic challenge. Thus, increasing the pool of energy reserves in the brain may prolong brain function during a variety of insults.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02429-03 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Coordinate Effects of Amphetamine on Brain Energy Metabolism and Protein Synthesis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Janet V. Passonneau	Chief, LNC	LNC	NINCDS
Other:	Thaddeus S. Nowak, Jr.	Staff Fellow	LNC	NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Cellular Neurochemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Effects of amphetamine on brain protein synthesis and energy metabolism are investigated in mice under conditions which give rise to changes in body temperature in response to the drug. Protein synthesis is assayed by an in vitro amino acid incorporation method developed in the laboratory to replace polyribosome profiles. Glycogen, glucose, phosphocreatine, and adenine and guanine nucleotides are measured enzymatically. During a period of drug induced hyperthermia, the inhibition of brain protein synthesis is tightly correlated with body temperature, inhibition occurring abruptly between 40° and 41°C. Brain glycogenolysis induced by the drug is more pronounced at elevated ambient temperatures, but does not correlate well with temperatures of individual mice. Through these and other observations, the reduction in brain protein synthesis by amphetamine can largely be dissociated from its effects on energy metabolism. Further studies will examine the possible activation of a translational inhibitor in extracts of hyperthermic animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02430-03 LNC

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Aspects of calcium metabolism in electric tissue

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: R. Wayne Albers Head, Section on Enzyme Chemistry LNC, IRP, NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neurochemistry

SECTION
Section on Enzyme Chemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.1	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Regulatory roles of calcium in Electrophorus electric organ are under investigation. The studies consist of two parts: (1) the isolation and purification of calmodulin from electric tissue; (2) isolation and characterization of a Ca-ATPase from electric tissue.

TAB 14 -- LABORATORY OF NEURO-OTOLARYNGOLOGY -- LNO/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Neuro-otolaryngology
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Neuro-otolaryngology, IRP
National Institute of Neurological and
Communicative Disorders and Stroke

Jörgen Fex, M.D., Ph.D., Chief

The Laboratory has continued its multidisciplinary approach with the focus on the inner ear and cochlear nucleus of mammalian species, of normal animals as well as of genetically deaf animals. The two Projects of the Laboratory have been advanced, these being Project Number Z01 NS 02216 07 LNO, Inner Ear Neuronal Mechanisms: A Multidisciplinary Analysis, respectively Project Number Z01 NS 02217 07 LNO, Synaptic Transmission and Neuronal Connections of the Mammalian Cochlear Nucleus. In particular, during this fiscal year, the Laboratory contributed with the following new knowledge.

We have extended our previous, published, immunocytochemical studies of the distribution of opioid peptides in the cochlea and have now findings indicating there are at least two different substances in the organ of Corti with enkephalin-like immunoreactivity. To complement these studies we have gone to other neuronal systems and have described in a published paper the first findings of enkephalin-like immunoreactive cells and fibers in a mammalian (guinea pig) retina. As a further complement to serve our ongoing studies of opioids in the cochlea and elsewhere in the nervous system we use high performance liquid chromatography (HPLC) and radio immuno assay (RIA) as techniques; a manuscript on HPLC identification of met-enkephalin in the inner ear has been submitted for publication.

Our immunocytochemical studies of the distribution of the two enzymes, aspartate aminotransferase and glutaminase, are ongoing and have continued to provide evidence for the hypothesis that these enzymes may serve as markers for neurons using the excitatory amino acids, glutamate and aspartate, as neurotransmitters. Our findings of the localization of aspartate aminotransferase in the cochlear nucleus, respectively in photoreceptors of the guinea pig, have been published, respectively have been submitted for publication. A report on aspartate aminotransferase in the guinea pig cochlea is in press. A manuscript on glutaminase as a marker for excitatory amino acid neurons in the auditory nerve and other regions is in preparation.

Immunocytochemical studies are being carried out on the distribution in the cochlea of the enzyme choline acetyltransferase; antisera against this enzyme have been received as gifts. The studies are expected to provide strong evidence concerning the cholinergic nature of the medial and the lateral efferent neurons of the organ of Corti.

We have studied how the apparently initially homogenous population of spiral ganglion cells of the immature cochlea develops into the two subpopulations of Type I and Type II cells of the adult cochlea; a manuscript is under preparation.

A neuropharmacological study is underway, using microiontophoretic techniques on synapses of cells of the cochlear nucleus in a brain slice.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02216 07 LNO

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Inner Ear Neuronal Mechanisms: A Multidisciplinary Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Fex	Chief, LNO	LNO NINCDS
	R. A. Altschuler	Staff Fellow	LNO NINCDS
	D. W. Hoffman	Staff Fellow	LNO NINCDS
	A. M. Schwartz	Staff Fellow	LNO NINCDS
	J. L. Mosinger	Guest Worker	LNO NINCDS

COOPERATING UNITS (if any)

F. Eckenstein, Max-Planck-Institute für Psychiatrie, Abteilung Neurochemie Am Klopfersptiz, D-8033, Martinsried, Germany

LAB/BRANCH

Laboratory of Neuro-otolaryngology

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.0	3.9	2.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long-range purpose of the project is to study the biochemistry, morphology, pharmacology and physiology of inner ear neurons and other cells and to describe the mechanisms of their interactions.

1. Immunocytochemical evidence indicates that at least two opioid peptides are present in the guinea pig cochlea. One of these is met-enkephalin, as indicated by biochemical studies using high performance liquid chromatography (HPLC) and radio immuno assay (RIA). 2. Complementing immunocytochemical studies have demonstrated the presence of enkephalin-like immunoreactivity in cells and nerve fibers in the guinea pig retina. 3. The study of the differential distribution of aspartate aminotransferase and glutaminase-like immunoreactivity at a high level in spiral ganglion cells in the modiolus and in nerve fibers and endings in the organ of Corti is ongoing. 4. An immunocytochemical study of the distribution of choline acetyltransferase in the cochlea has been initiated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER ZO1 NS 02217 07 LNO

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Synaptic Transmission and Neuronal Connections of the Mammalian Cochlear Nucleus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Fex	Chief, LNO	LNO NINCDS
	R. A. Altschuler	Staff Fellow	LNO NINCDS
	M. R. Martin	Senior Staff Fellow	LNO NINCDS
OTHER:	J. P. Donoghue	Staff Fellow	LNP NIMH

COOPERATING UNITS (if any) C. W. Cotman, Dept. Psychobiol., Univ. Calif, Irvine, CA 92717; T. Hökfelt, Fogarty Scholar, N.I.H., Dept. Histol., Karolinska Inst., Stockholm, Sweden; N. Curthuys, Dept. Biochem., Univ. Pittsburgh, Pittsburgh, PA; R. J. Wenthold, Dept. Neurophysiol., Univ. Wisconsin, Madison, Wisconsin 53706

LAB/BRANCH
Laboratory of Neuro-otolaryngology

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.6	1.7	1.9

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to study the biochemistry, morphology, pharmacology and physiology of synaptic transmission and neuronal connection of nerve cells of the mammalian cochlear nucleus: 1. Complementing previously published findings on the cytochemically localized aspartate aminotransferase-like immunoreactivity we have now found highly concentrated such activity in photoreceptors of the guinea pig. 2. Synapses between the auditory nerve and cells in the cochlear nucleus are being studied in vitro, using microiontophoretic techniques applied to a brain slice preparation.

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Neuropathology and Neuroanatomical Sciences
National Institute of Neurological and Communicative disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Neuropathology and Neuroanatomical Sciences, IRP
National Institute of Neurological and Communicative Disorders and Stroke

Igor Klatzo, Chief

The main accomplishments in the LNNS during the past year were as follows:

The Section on Cerebrovascular Pathology made significant progress in elucidation of the pathophysiology of the blood-brain barrier (BBB) in cerebral ischemia. A biphasic character of BBB breakdown following release of ischemic occlusion was demonstrated in two different models. In cats subjected to one hour of middle cerebral artery (MCA) occlusion, the first opening of the barrier occurred shortly after recirculation and was related to high elevations of the regional cerebral blood flow (rCBF), measured by hydrogen clearance method with platinum-coated electrodes implanted bilaterally into the caudate nucleus and the Sylvian cortex. Following this, there was a refractive period during which no BBB leakage could be demonstrated in spite of extremely low rCBF values during ischemic occlusion and very pronounced reactive hyperemia following recirculation. The second opening of the barrier was observed after 5 hours of recirculation at which time there was a conspicuous ischemic damage of the tissue. Both openings of the BBB were observed only when the drop of rCBF during ischemia reached below 12 ml/100 g/min threshold values. Similar biphasic breakdown of the BBB was observed also in gerbils subjected to bilateral 5-minute occlusion of the common carotid arteries. The first opening was demonstrated with horseradish peroxidase tracer, immediately following release of occlusion, and it was associated with patchy foci of hyperemia shown by application of Sokoloff's ^{14}C iodoantipyrine radioautographic method and with ^{3}H nicotine assays. The second opening of the barrier was observed 3 days after recirculation and coincided with severe ischemic cell damage in the CA1 sector of the hippocampus.

Studies on bilateral 5-min carotid occlusion in gerbils provided insight into several aspects of pathophysiology of cerebral ischemic injury. First of all, it demonstrated features of selective vulnerability expressed in a different character of ischemic injury in various sectors of the hippocampus. The most interesting were changes in CA1 neurons which for 2 days appeared structurally intact and then on the 3rd day the neurons showed rapid disintegration. During the first two days after recirculation there was evidence of uncoupling between rCBF and glucose utilization as assessed by the radioautographic methods of Sokoloff. At the same time spontaneous electrical activity recordings with microelectrodes from the CA1 sector and the cerebral cortex revealed a greatly increased neuronal activity in the former.

Investigations on the dynamics and pathophysiology of ischemic brain edema were continued in cats subjected to the MCA occlusion. Correlative evaluation of the rCBF changes, behavior of the BBB, and water content changes by specific gravity measurements were supplemented by measurements of electrical impedance in the ischemic regions by chronic implantation of electrodes. With this approach it is possible to follow development of the cytotoxic ischemic edema indicated by progressive increase in impedance. Also possible to determine with impedance measurement is the event of increased vascular permeability and dilatation of extracellular spaces. It is expected that forthcoming data on electrical impedance will essentially contribute to better understanding of the pathomechanisms of ischemic brain edema.

The continuous goals of the Section on Neurocytobiology have been: A) to develop and utilize new model systems for the investigation of basic mechanisms operative on the level of normal and pathologically altered blood-brain barrier (BBB); B) to study the metabolic processes occurring in cerebral ischemia and ischemic edema especially their prevention and therapy.

In studies related to BBB in cerebral endothelial cultures the establishment of metabolically active endothelial cells in culture provided a new "living" model system for the study of cerebroendothelial properties and the regulatory mechanism of their function and its relationship to BBB. These investigations showed that the capillary endothelial cells contain a specific β_2 and α_2-adrenergic sensitive adenylate cyclase (AC). The presence of α_2-type receptors is of special interest since they were so far associated with the smooth muscle function only. Their existence on the endothelial level is compatible with the recent concept of α-adrenergic receptors' participation in the central regulation of blood pressure.

Among the effects of various tested hormones, PGE_1 and PGE_2 (prostaglandins) were found to be the most potent AC activators, while adenosine, angiotensin I and II, GABA and VIP inhibited the enzyme activity. However, acetylcholine, histamine, serotonin, glycine, glutamine, bradykinin, neurotensin and vasopressin did not influence the AC activity in the disrupted cultured endothelial cells. The susceptibility of the cerebrovascular endothelial AC system to the vasoactive substances as well as the presence of β_2 and α_2-type adrenergic receptors linked to AC in the cultured endothelium provides support for the proposed endothelial involvement in the regulation of cerebrovascular permeability, blood flow and blood pressure.

The presence of phenylethanolamine-N-methyltransferase (PNMT), a catecholamine synthesizing enzyme which converts norepinephrine to epinephrine in the endothelial cell cultures and cerebral microvessels was demonstrated by biochemical and immunocytochemical techniques. Until now, the activity of this enzyme was associated with the brain regions containing catecholaminergic cell bodies. Thus, the demonstration of PNMT in the capillary endothelium, an extraneuronal compartment, indicates that the microvessels themselves are capable of synthesizing epinephrine from norepinephrine, although the function of the formed monoamine is unknown. Since the vascular adrenergic innervation has been implicated in the regulation of BBB permeability and cerebral blood flow, it is possible that the synthesized epinephrine in the microvessels might participate in the regulation of cerebral vascular permeability and/or blood flow as one of the substrates necessary for autoregulation or for the metabolic integrity of the BBB.

In studies in gerbils on cerebral ischemia, its pathophysiology, prevention and therapy - a continuous evaluation of the effects of naturally occurring central nervous system depressant [γ-butyrolactone (GBL) and γ-hydroxybutyrate (GHB)] on cerebral ischemia has been focused on the elucidation of the possible mechanisms responsible for the observed beneficial effect of GBL and GHB on ischemic brain edema. During these studies an accumulation of free tryptophan was found in the brain along with decreased levels of monoamines (5-HT and NE) and increased concentrations of their metabolites in the first phase of ischemic edema. GHB treatment prevented the cerebral accumulation of free tryptophan, 5-HIAA and HVA. Moreover, it diminished the loss of NE and stabilized the 5-HT content of the brain. The investigation in gerbils concerned with the ischemic effect on the β-receptors suggested a change in sensitivity of the β-receptors to catecholamine and an alteration of GTP regulatory site of the β -receptors in the brain subjected to ischemia.

In the Section on Cellular Neuropathology, investigators used immunocytochemical methods to study the distribution of viruses, myelin proteins, and glial constituents in experimental and human demyelinating diseases.

In two projects, distributions of myelin-associated glycoprotein (MAG), an oligodendroglial constituent, and basic protein (BP), a compact myelin component were compared. In hexachlorophene intoxication, CNS myelin sheaths become vacuolated. Splitting of compact myelin layers occurs as intramyelinic edema progresses but myelin sheath breakdown is uncommon and if hexachlorophene administration is stopped, the process is reversible. In these lesions, MAG-stained periaxonal processes of oligodendroglia remain normal suggesting that these processes and this glycoprotein have an important role in the interactions needed for myelin sheath maintenance and repair. Progressive multifocal leukoencephalopathy (PML) is a papova virus infection of oligodendroglia that produces myelin breakdown in patients with defective immune responses. In PML, histologically identified zones of myelin breakdown correspond closely to areas in adjacent sections with absent or abnormal BP staining. But zones of decreased MAG staining are much larger and extend into normal appearing white matter that surrounds demyelinated areas. Here, the density of virally infected oligodendroglia is highest suggesting that altered MAG staining is a sign of early oligodendroglial abnormalities that precede and may cause myelin breakdown. It is of interest that patterns of MAG and BP staining in multiple sclerosis (MS) resemble that seen in PML, suggesting that oligodendroglia may be the primary target in MS. A different pattern is seen in both acute and chronic relapsing EAE.

Another important project has demonstrated that the MS strain of type 2 herpesvirus can produce spinal cord and optic nerve demyelination when injected intracerebrally into mice. Types of lesions seen and their distribution are age and dose-dependent. Typical herpesvirus particles are found in glial cells located in acute lesions; later, fewer virions are present. This is the first experimental demyelinating disease that has been produced with a virus known to cause human disease and will serve as an important model to study how viruses produce myelin breakdown.

Finally, electron microscopic immunocytochemical methods and tissue preparative techniques have been modified to study the localization of proteins in myelin's lamellar structure. In the project, BP has been localized in dense

line regions of both CNS and PNS myelin, a site favored also by indirect evidence from biochemical experiments. The modifications created for BP localization will be useful in electron microscopic studies of other myelin constituents.

The goal of the Section on Functional Neuroanatomy is to investigate important problems in cellular neurobiology by means of modern structural techniques. In the course of studying release of transmitter at synapses, an important technique for freezing tissue directly was developed. These studies of transmitter release have been completed, and our current program depends on exploring several new avenues opened by the freezing technique.

The first advantage of the direct freezing technique is that rapid structural changes can be stopped with a msec time resolution. In the last year, papers have been published showing the fate of synaptic vesicle membrane following exocytotic transmitter release, and how exocytosis begins as a punctate rearrangement of the plasma membrane in a secretory cell. Differences between the membrane ultrastructure of synapses on tonic (slow) muscle fibers and twitch (fast) muscle have been found in two different species.

Direct freezing can also be used to visualize intrinsic membrane proteins in greater detail and closer to their natural state. For this purpose a special apparatus has been developed to freeze-fracture tissue at temperatures near absolute zero (10°K). This approach prevents many of the structural changes which normally occur during fracturing and shadowing. Application of this technique to open and closed channels ("connexons") at gap junctions shows new structural details which change depending on their functional state. The substructure of membrane particles at acetylcholine receptors, SR-T junctions in muscle, tight junctions, and in astrocyte membranes involved in the blood-brain barrier are being examined. Lipid polymorphism turns out to make an important contribution to membrane structure at tight junctions, and the contribution of such nonbilayer lipid organization at gap junctions and at sites of membrane fusion is being explored. One criterion for recognizing lipid polymorphism in membranes is to find structures in liposomes similar to the naturally occurring structures.

The new freeze-fracture technique allows the cytoskeleton of axons to be visualized without any of the chemical pretreatments that have been used up to now to prepare cytoskeletons. Organelles involved in axoplasmic transport are situated in special "compartments" of the axoplasm, and each type of organelle has characteristic relationships with cytoskeletal elements. This approach has also been applied to show the relationships of the cytoskeleton to the postsynaptic membrane of auditory brain stem synapses. Fine filaments connect components of the postsynaptic membrane, believed to be receptors, with a microfilament network lying in the cytoplasm beneath the synapse. This finding explains the long-term stability of the postsynaptic region of the neuronal membrane. Recently, monolayers of cultured cells are being frozen after observing them with light microscopical methods and then examined in a 200 KV electronmicroscope to determine: how organelles move through axoplasm; the relationships of membrane turnover to the cytoskeleton in growth cones; and the relationships between acetylcholine receptor clustering and the cytoskeleton in cultured myocytes.

Another advantage of the freezing technique is that soluble components of the cell interior are preserved in their natural positions. Methods have been developed to use cryopreparation to measure the distributions of elements, particularly calcium, in rapidly frozen tissue by means of analytical electron microscopical techniques. The initial aim of developing these methods was to examine the redistribution of calcium during exocytosis at synapses and secretory cells. Now, that the major technical obstacles to these original goals have been surmounted, any element can be measured in small regions of cells (20 nm) with the time resolution afforded by rapid freezing (1-2 msec). Specific aims are to determine whether presynaptic active zones are sites for calcium entry during evoked transmitter release, and also to determine the site and role of internal calcium stores in secretion. The results, so far, have provided evidence that the endoplasmic reticulum is a major calcium buffering system in nerves and secretory cells. Also, it becomes apparent that secretory granules in various cells store calcium and may even release it during exocytosis.

The Section on Neurocytology continued to explore the interactions between allografts of peripheral and central nervous tissue to brain surfaces, the behavior of a glycolytic enzyme in regenerating neurons and the responsiveness of certain particles within the plasma membrane of astrocytes. The neurotropic effect exerted by transplants of superior cervical ganglion (SCG) has now been found to include the interneurons and astrocytes of the olfactory bulb. By placing an SCG graft on the dorsal surface of the bulb in 6-day-old rat recipients, the granule cells and, probably, periglomerular and tufted neurons, migrate anomalously toward the graft. Induction of post-natal, aberrant migration of neurons is beginning to appear as a general effect on certain interneurons. The availability of synaptic targets determined the number of surviving ganglion cells in the transplant. By removing the host's own SCG ganglia bilaterally at the time of transplantation, the ganglia's targets: blood vessels of the pia and choroid plexus, were denervated and thus became available to regenerating neurites. As a result, the number of surviving neurons was increased about 7-fold in a 6-month-old graft. These results emphasized the importance of providing available, specific targets for the long-term survival of neuronal grafts. A consequence of by-passing the blood-brain and blood-CSF barriers to horseradish peroxidase (HRP) through SCG grafts was a rapid and pronounced uptake of the glycoprotein by the astrocytes (Golgi epithelial cells) of the cerebellum. This uptake appeared to be stimulated by the presence of the graft. The gliotropic effect of the SCG may now be taken to include augmented endocytosis.

In regenerating hypoglossal neurons, there was a very modest but consistent increase in non-neuronal enolase (NNE) and a concomitant marked fall in neuron-specific enolase (NSE), detected immunocytochemically. There appeared to be, therefore, a conversion to the fetal ratio of these isoenzymes during regeneration of a cranial nerve. There was also found a target-dependent recovery of NSE levels. If, after axotomy, the proximal and distal stumps of the XII nerve are anastomosed, the NSE level largely recovered by 60 days. If, instead, the proximal stump was inserted into an inappropriate muscle so that reinnervation does not take place, the levels of NSE remained low. These results are the first to show that the levels of a neuronal glycolytic enzyme are not necessarily influenced by regeneration alone, but rather by some signal from the target muscle.

The responses of assemblies, the orthogonal aggregates of particles within the plasma membranes of astrocytes, have been further elucidated. At the periphery of a cold lesion of the cerebral cortex in young rats, the assemblies within astrocytes began to increase within 30 minutes and, by 4 to 6 hours, were 4 to 5 times higher than control values. Catabolites, such as CO_2, also augmented the number of assemblies four-fold within 30 minutes. Weak acids, such as lactate caused a rearrangement of assemblies, whereas acetic and proprionic brought about a marked decrease in number. These results demonstrated rapid changes in the astrocyte membrane to catabolites such as CO_2, and lactate, which accumulate during ischemia. These alterations are part of a rapidly developing and incipient stage of reactive gliosis, hitherto unknown.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02456-02 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
The regional selectivity of blood-brain barrier (BBB) changes induced by various epileptogenic agents and acute hypertension

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Nitsch	Visiting Scientist	LNNS NINCDS
Other:	K. Fujiwara	Visiting Fellow	LNNS NINCDS
	H. Laursen	Visiting Associate	LNNS NINCDS
	R. Suzuki	Visiting Fellow	LNNS NINCDS
	P. Ting	Expert	LNNS NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02457-02 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Regional cerebral blood flow (rCBF) changes in variously induced epileptiform seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Nitsch	Visiting Scientist	LNNS NINCDS
Other:	R. Suzuki	Visiting Fellow	LNNS NINCDS
	P. Ting	Expert	LNNS NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02458-02 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Changes in specific gravity (SG) of rabbit brain tissue during drug-induced epileptiform convulsions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Nitsch	Visiting Scientist	LNNS NINCDS
Other:	K. Fujiwara	Visiting Fellow	LNNS NINCDS
	T. Kuroiwa	Visiting Fellow	LNNS NINCDS
	R. Suzuki	Visiting Fellow	LNNS NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02545-01 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Changes of spontaneous neuronal activity of cortical and hippocampal CA1 neurons following 5 minute ischemia in gerbils

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Suzuki	Visiting Fellow	LNNS NINCDS
Other:	T. Yamaguchi	Visiting Fellow	LNNS NINCDS
	C.-L. Li	Medical Officer	SN NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	1.0	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Activity of cortical neurons and hippocampal CA1 neurons was recorded during 5 minute forebrain ischemia and following recirculation in gerbils. Spontaneous activity in both cortical and CA1 neurons ceased to appear within 60 sec of the onset of ischemia and it began to reappear 10-20 min after recirculation. Furthermore, during 24 hrs a considerable number of CA1 neurons showed hyperactivity as shown by an increase in spike discharges. However, on the second day of ischemia CA1 neurons became completely silent, although histological sections showed a relatively good preservation of their cellular structure.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02546-01 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Behavior of the blood-brain barrier (BBB) and the regional cerebral blood flow (rCBF) in cerebral ischemia produced by middle cerebral artery (MCA) occlusion in cats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. Kuroiwa	Visiting Fellow	LNNS NINCDS
Other:	P. Ting	Special Expert	LNNS NINCDS
	T. Yamaguchi	Visiting Fellow	LNNS NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.4	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Two independent openings of the BBB were demonstrated following one hour MCA occlusion in cats. The first opening occurred shortly after release of occlusion and was associated with high elevations of the rCBF. The second opening of the barrier was demonstrable after 5 hours following release of occlusion and was associated with severe ischemic tissue changes. Both openings of the barrier were dependent on the rCBF falling below threshold values (12 ml/100 g/min) during the occlusion.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02547-01 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Observations on behavior of the blood-brain barrier (BBB), regional cerebral blood flow (rCBF) and glucose utilization in gerbils subjected to 5 min bilateral occlusion of the common carotid arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Suzuki	Visiting Fellow	LNNS NINCDS
Other:	T. Yamaguchi	Visiting Fellow	LNNS NINCDS
	F. Orzi	Visiting Fellow	LCM NIMH
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
Laboratory of Cerebral Metabolism, NIMH

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	1.0	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

BBB, rCBF and glucose utilization (GU) were compared in gerbils during 5 min cerebral ischemia and after recirculation. There was an increased permeability of the BBB shortly after release of the circulation and this was correlated with patches of hyperemia demonstrated in rCBF radioautography. Ten minutes after release of occlusion there was a pronounced hypoperfusion expressed in markedly reduced rCBF values. This was associated with conspicuous increase in glucose utilization in the hippocampus which lasted for 24 hours and then became greatly reduced when assayed at 48 hours. Secondary breakdown of the BBB was observed 3 days after release of occlusion in the hippocampus and this coincided with severe ischemic damage of the CA1 neurons.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02548-01 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Evaluation of electrical impedance in the cerebral ischemia produced by occlusion of the middle cerebral artery (MCA) in cats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Ting	Special Expert	LNNS NINCDS
Other:	H. Wagner	Chief, Neuronal Interactions Section	LNP NINCDS
	T. Yamaguchi	Visiting Fellow	LNNS NINCDS
	T. Kuroiwa	Visiting Fellow	LNNS NINCDS
	R. Cahn	Visiting Fellow	LNNS NINCDS
	I. Klatzo	Chief, Lab. Neuropath. Neuroanat. Sci.	LNNS NINCDS

COOPERATING UNITS (if any)
Laboratory of Neurophysiology, NINCDS

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Cerebrovascular Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	1.9	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The changes in electrical impedance were studied in cats subjected to left MCA occlusion, either permanent or followed by the release of occlusion. The main findings indicate that shortly following MCA occlusion there is a progressive increase in impedance, reflecting the onset of cytotoxic edema in the ischemic regions. The breakdown of the BBB is reflected in decrease of impedance. The correlation of impedance measurements with those of rCBF in the same experiment should greatly elucidate the dynamics of ischemic brain edema.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02275-06 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Cerebral capillary endothelial cultures: Response to vasoactive substances.
[Former title: Cerebral capillary endothelial cultures]

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Spatz	Head, Section on Neurocytobiology	LNNS NINCDS
	I. Karniouchina	Visiting Fellow	LNNS NINCDS

COOPERATING UNITS (if any)
Dr. Lawrence DeBault, Department of Pathology, Children's Hospital, Oklahoma City, Oklahoma

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	0.7	0.9

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The established cerebral endothelial cell cultures derived from dissociated cerebral microvessels possess β_2 and α_2-adrenergic sensitive adenylate cyclase (AC). The endothelial AC system was also found to be stimulated by prostaglandins E_1 and E_2.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02324-05 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Studies on the blood-brain barrier (BBB) to 5-hydroxytryptamine and norepinephrine metabolites: Cerebral capillary endothelial culture metabolism and synthesis of 5-hydroxytryptamine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Spatz	Head, Section on Neurocytobiology	LNNS NINCDS
Other:	C. Maruki	Visiting Fellow	LNNS NINCDS

COOPERATING UNITS (if any)
Dr. Ikuko Nagatsu, Department of Anatomy, Fujita-Gakuen University School of Medicine, Toyoake, Aiche 470-11, Japan

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Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.3	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cerebral endothelial cultures derived from 2-day-old rats and propagated for 7-10 weeks showed the capability not only of taking up and metabolizing 5-HT but also of synthesizing this amine.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02327-05 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
The study of monoamines' uptake and pinocytotic activity of pia arachnoid cultures.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. Spatz Head, Section on Neurocytobiology LNNS NINCDS

COOPERATING UNITS (if any)
Dr. H. Hervonen, Department of Biomedical Sciences, University of Tampere, Tampere, Finland

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been temporarily discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02357-04 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

The therapeutic γ-hydroxybutyrate effect on experimental cerebral ischemia in Mongolian gerbils

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Spatz	Head, Section on Neurocytobiology	LNNS NINCDS
Other:	C. Maruki	Visiting Fellow	LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.3	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The γ-hydroxybutyrate (GHB) amelioration of ischemic cerebral edema (cytotoxic type) correlated well with the stabilization of monoamines' synthesis and metabolism, especially that of 5-HT.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02361-05 LNNS

PERIOD COVERED
October 1, 1981 tto September 30, 1982

TITLE OF PROJECT (80 characters or less)
Investigations on blood-brain barrier (BBB) permeability

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. Spatz Head, Section on Neurocytobiology LNNS NINCDS

COOPERATING UNITS (if any)
Prof. K. G. Go and Dr. H. J. Hauthof, Departments of Neurosurgery and Pathology, University of Groningen, The Netherlands

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The enhancement of serum protein permeability was investigated in bilateral cerebral ischemia induced by occlusion of both carotid arteries for 15 minutes. The demonstration of extravasated protein depended on the protein marker used. The most sensitive protein tracer was found to be the serum antibodies (IgG class) to horseradish peroxidase.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02462-02 LNNS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biochemistry of brain ischemia and ischemic edema in Mongolian gerbils: beta-adrenergic receptor studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	I. Karniouchina	Visiting Fellow	LNNS NINCDS
Other:	C. Maruki	Visiting Fellow	LNNS NINCDS
	M. Spatz	Head, Section on Neurocytobiology	LNNS NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	0.8	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The pathogenetic investigations of cerebral ischemia have been concerned with determining the effect of this process on the neurotransmitter receptors, in particular the beta-adrenergic type; these studies have shown that brain ischemia affects the membrane affinity for ^{3}H dihydroalprenolol (^{3}H-DHA) binding sites due to a decreased association but not dissociation rate of the ligand to the beta-receptors.

This study was presented at the 3rd Belgrade Symposium on Developmental and Circulatory Aspects of Brain Metabolism, and the proceedings will be published by the Plenum Press. This project has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02463-02 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
The effect of central nervous tissue on cerebral endothelial properties

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. Spatz Head, Section on Neurocytobiology LNNS NINCDS

COOPERATING UNITS (if any)
Dr. Ronald F. Dodson, Division of Experimental Pathology, East Tyler Chest Hospital, Tyler, Texas

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been temporarily discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02552-01 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Investigation of extraneuronal catechol synthesizing enzymes in the central nervous system

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Spatz	Head, Section on Neurocytobiology	LNNS NINCDS
Other:	C. Maruki	Visiting Fellow	LNNS NINCDS

COOPERATING UNITS (if any)

Dr. Ikuko Nagatsu, Department of Anatomy, Fujita-Gakuen University School of Medicine, Toyoake, Aiche 470-11, Japan

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	0.5	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Immunohistochemical and biochemical studies of cerebral microvessel and cerebrovascular endothelial cultures showed the presence of phenylethanolamine-N-methyltransferase (PNMT) activity in both tissues. These findings indicate that the extraneuronal tissue contains a catecholamine synthesizing enzyme which is responsible for conversion of norepinephrine to epinephrine.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01995-10 LNNS

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Morphological studies of myelin formation, breakdown and regeneration

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	H. deF. Webster	Associate Chief	LNNS NINCDS
Other:	H. Shii	Visiting Fellow	LNNS NINCDS
	F.X. Omlin	Guest Worker	LNNS NINCDS
	J.R. Martin	Senior Staff Fellow	LNNS NINCDS
	G.L. Stoner	Senior Staff Fellow	LNNS NINCDS
	H. Lassmann	Associate professor	Univeristy of Vienna Medical School, Vienna, Austria
	E.P. Richardson Jr.	Professor	Massachusetts General Hospital, Boston, MA

COOPERATING UNITS (if any) Neurological Institute, University of Vienna Medical School, Vienna, Austria; Department of Neuropathology and Neurology, Massachusetts General Hospital, Boston, Massachusetts

LAB/BRANCH Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION Section on Cellular Neuropathology

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 6.2	PROFESSIONAL: 3	OTHER: 3.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long range goal of this project is to combine immunocytochemical methods with light and electron microscopy to study cellular mechanisms of myelin formation, breakdown and regeneration. Nervous tissues from experimental animals have been studied in the following current projects: 1) Distribution of myelin-associated glycoprotein (MAG) and basic protein (BP) in chronic relapsing experimental allergic encephalomyelitis (EAE), an animal model for multiple sclerosis (MS); 2) Electron microscopic immunocytochemical localization of basic protein in the Lamellar structure of myelin; 3) Electron microscope and immunocytochemical studies of abnormal axon-glial relationships in jimpy mice (mutants with a severe defect in CNS myelin formation).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02549-01 LNNS

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Animal Models of Herpesvirus-induced demyelination and relation to human disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.R. Martin	Senior Staff Fellow	LNNS NINCDS
Other:	G.L. Stoner	Senior Staff Fellow	LNNS NINCDS
	H.deF. Webster	Associate Chief	LNNS NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION Section on Cellular Neuropathology

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.1	PROFESSIONAL: 1	OTHER: 2.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The main objective of this research project is to look for evidence which links herpesvirus infections, especially herpes simplex virus type 2 (HSV-2), to human neurological disease, particularly multiple sclerosis. Thus far, these studies have included: 1) A comparison of the epidemiology of herpes simplex virus types 1 and 2 and that of multiple sclerosis, and 2) A search for CNS demyelination in experimental HSV-2 infections, and initial studies of the conditions which favor development of this pathology.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02550-01 LNNS

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biochemical and immunologic mechanisms in virally-induced CNS demyelination

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.L. Stoner	Senior Staff Fellow	LNNS NINCDS
Other:	J.R. Martin	Senior Staff Fellow	LNNS NINCDS
	H.deF. Webster	Associate Chief	LNNS NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION

Section on Cellular Neuropathology

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The first phase of this work has concentrated on the preparation of antisera to Herpes simplex virus types 1 and 2 for use in the peroxidase-antiperoxidase (PAP) immunocytochemical technique. Antisera have been obtained which can differentiate the two types of HSV in paraffin sections of infected mouse CNS. Expression of viral antigens will be studied in the CNS of unimmunized mice and of mice immunized with the homologous or heterologous HSV type. The long range goal of this project is the understanding of the mechanisms of demyelination in viral infections of the CNS, the mechanisms of immunity to these infections, and the relationship between these two phenomena.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01442-16 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Permeability of Cellular Layers in the Vertebrate Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. S. Reese	Head, Section on Functional Neuroanatomy	LNNS NINCDS
Other:	B. Kachar	Visiting Fellow	LNNS NINCDS

COOPERATING UNITS (if any)

R. P. Rand, Brock University, Ontario

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Functional Neuroanatomy

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The substructure of tight junctions is investigated by direct freezing techniques that avoid any chemical fixation and serve to increase the resolution of individual membrane components. The backbone of the tight junction is a pair of rod-shaped structures embedded in the central lipophilic domain of each of the paired component membranes. This conclusion replaces the previous view that tight junctions are comprised of rows of intramembrane proteins. Instead, the rod-shaped structures, which are comparable to cylindrical micelles in liposomes, are now interpreted as inverted cylindrical micelles of membrane lipids. These results lead to an understanding of how tight junctions serve in the blood-brain barrier system to prevent small charged solutes from entering the brain. Similar techniques are being applied to understand the substructure of specific glial membrane structures which are regarded as components of the blood-brain barrier system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01881-12 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Structural basis of synaptic transmission.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. S. Reese	Head, Section on Functional Neuroanatomy	LNNS NINCDS
Other:	C. P. Ko	Guest Worker	LNNS NINCDS
	K. J. Lynch	Guest Worker	LNNS NINCDS
	R. L. Ornberg	Staff Fellow	LNNS NINCDS
	D. W. Pumplin	Guest Worker	LNNS NINCDS
	V. Verma	Visiting Fellow	LNNS NINCDS
	J. Walrond	Staff Fellow	LNNS NINCDS

COOPERATING UNITS (if any)
T. Sejnowsky, Neurobiology Dept. Harvard Medical School
S. Nakajima, Purdue University, West Lafayette, IN
R. L. Gulley, Lab. Neuro-otolaryngology, NINCDS

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Functional Neuroanatomy

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7.5	5.0	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project seeks to determine the location and mechanism of neurotransmitter secretion. Rapid freezing and subsequent freeze-fracture of synapses capture fleeting structural changes in the cell membrane accompanying discharge of synaptic vesicles. By these means, the prodromata and aftermath of synaptic vesicle exocytosis have been determined. This approach has been extended to other secretory cells where details surrounding the initiation of secretion are more readily studied. New methods have been developed to use rapid freezing to determine how the distribution of intracellular calcium changes in different functional states. Organelles which store and release calcium during secretion as well as sequestering it afterwards have been found. This work is significant in that it defines the dynamic structure of normal synapses by relating normal variations in structure to different functional states. The current program also includes freeze-fracture of developing and degenerating synapses; the results will aid in understanding of normal development as well as the effects of diseases and developmental failures on synaptic structure in the brain and peripheral nervous system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02551-01 LNNS

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Structure of Neuronal Cytoplasm

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. S. Reese	Head, Section on Functional Neuroanatomy	LNNS NINCDS
Other:	Gadi Benshalom	Visiting Fellow	LNNS NINCDS
	Paul Bridgman	Guest Worker	LNNS NINCDS

COOPERATING UNITS (if any)

Bruce Schnapp, Queen Square, London, England

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Functional Neuroanatomy

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This new project seeks to determine the structure of neuronal and glial cytoplasm particularly as it pertains to axoplasmic transport, secretion, cell movement, and the organization of the cell surface. Living cells or tissues are directly rapid-frozen and the structure of their cytoplasm is determined by one of two methods, freeze-etching or freeze-substitution. Axons in turtle optic nerves have different axoplasmic domains, each characterized by specific types of filaments and by its content of organelles. In other experiments, cultured myocytes grown on grids, frozen, and freeze-substituted are examined directly at high voltages in an electromicroscope. So far, it has been shown that the cytoplasmic anlage consists of fine filaments instead of a microtubular meshwork. We plan to use this direct method of observing the cytoskeleton to observe the relationship to the cytoskeleton of organelles moving by fast axoplasmic transport, and to observe how the cytoskeleton changes near aggregations of receptors at post synaptic membranes in developing synapses.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01805-14 LNNS

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Membrane Structure of Astrocytes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. J. Anders	Expert Consultant	LNNS NINCDS
	M. W. Brightman	Head, Section on Neurocytology	LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	1.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The assemblies or orthogonal aggregates of particles within the cell membrane of astrocytes increase in number at the periphery of a cold lesion of the cerebral cortex in 9 day-old rats within 30 minutes. By 4 to 6 hours following the lesion, the number of assemblies is 4 to 5 times greater than that of resting astrocytes. Hypercapnia also leads to a marked and rapid augmentation. Within 30 minutes, there is a four-fold rise in assembly number. Weak acids, such as acetic and proprionic, when added to the culture medium, result in a decrease of about 10 to 3-fold, respectively, in the assembly number in astrocytes maintained in vitro for 14 days. Lactic acid did not appear to cause a significant change in the number of assemblies, but did cause them to aggregate. Etching of the uncleared astrocyte surface exposed to the lectin, concanavalin A, did not result in capping of surface particles, a finding which implies that the assemblies may not have an extrinsic, carbohydrate component.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02086-09 LNNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regeneration in Peripheral and Central Nerves

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. Kirino	Visiting Fellow	LNNS NINCDS
Other:	J. Rosenstein	Guest Worker	LNNS NINCDS
	D. Pagnanelli	Guest Worker	LNNS NINCDS
	M. Brightman	Head, Section on Neurocytology	LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.4	2.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Neuronotropic effect of superior cervical ganglion (SCG) grafts has been extended to the olfactory bulb, where granule cells and, possibly, other interneurons migrate anomalously and postnatally toward the graft. The column of migrating cells incudes astrocytes which migrate with microglial cells and neurons to push aside glomeruli. Within the transplant, the number of neurons that survive depends on the availability of target tissue: the blood vessels of the pia and choroid plexus. Bilateral removal of the rat's own SCG at the time of transplantation increases the number of surviving ganglion cells about 4-fold during the first month and about 7-fold during the sixth month after grafting. In regenerating hypoglossal neurons of monkeys, there is a very modest rise in non-neuronal enolase concurrent with a pronounced fall in neuron-specific enolase (NSE). If the regenerating nerve, in rats, is allowed to reinnervate the tongue, the level of NSE approaches near-normal levels in 60 days. If the nerve is prevented from doing so, the NSE level remains low.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02144-08 LNNS

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Blood-Brain Barrier and Ganglion Implants.
Former Title: The Blood-Brain Barrier. Bypassed With Ganglion Implants.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. W. Brightman	Head, Section on Neurocytology	LNNS NINCDS
Other:	J. Rosenstein	Guest Worker	LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION Section on Neurocytology

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	.9	.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

No fenestrated endothelium -induced or invasive- that could exude hematogenous horseradish peroxidase (HRP), has been found in the cerebral tissue adjacent to grafted superior cervical ganglion. The extracellular route taken by blood-borne HRP, from permeable vessels of the graft to brain extracellular fluid, has thus been confirmed. However, the non-fenestrated endothelium of capillaries in the brain adjacent to the graft has many more pits and vesicles than that of neighboring regions; most of them become labeled with HRP coming from the blood itself and the cerebral extracellular clefts. Some of the HRP that escapes from the fenestrated vessels of the graft, enters the subarachnoid space from which it is endocytosed by the bordering astrocytic end-feet adjacent to the graft. The HRP is then transported retrogradely to lysosomes within the astrocyte cell body. The sharply demarcated line of labeled astrocytes stands in sharp contrast to the unlabeled glial cells on either side. Even without HRP, the lysosomes in the soma of astrocytes adjacent to the graft, are far more numerous and larger than those of its neighbors, presumably due to the repeated uptake of cellular debris from the ganglion cells that have not found targets and that, consequently, have degenerated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02286-06 LNNS

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mechanism of Cerebral Hemorrhages

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. Cammermeyer Guest Worker LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Office of the Chief, LNNS

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Petechial cerebral hemorrhages induced by oil embolism in material fixed by perfusion are compared with those in material fixed by immersion.

This project has been completed and the manuscript is being prepared for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02362-04 LNNS

PERIOD COVERED October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Effect of dimethyl sulfoxide on the histochemical demonstration of glycogen in the perfusion-fixed brain.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. Cammermeyer Guest Worker LNNS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION

Office of the Chief, LNNS

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

When normal Netherlands dwarf rabbits were perfused with dimethyl sulfoxide (DMSO)-containing solutions, the brains exhibited pericapillary foci with acute tissue destruction and perivenous areas in which neurons were filled with glycogen. Glycogen was also discernible in mi oglial cells and oligodendrocytes. Because of the irregular distribution of glycogen-filled cells, this method of fixation is not recommended for systematic studies on the distribution of glycogen in normal and experimental animals. This project has been completed and the manuscript is being prepared for publication.

TAB 16 -- LABORATORY OF NEUROPHYSIOLOGY -- LNP/IRP

ANNUAL REPORT

October 1,1981 through September 30, 1982

Laboratory of Neurophysiology

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Laboratory of Neurophysiology
National Institute of Neurological and
Communicative Disorders and Stroke

Chief

Jeffery L. Barker, M. D.

In July, 1981 the Administrators of the Intramural Program of the NINCDS appointed a permanent Chief to lead the Laboratory of Neurophysiology. He has proposed a multi-disciplinary program designed to study the biological properties of specific types of nerve cells resident in the mammalian CNS. Several rooms have been renovated, the appropriate equipment requisitioned, and some of the personnel integral to the program appointed. At the same time principal investigators and their collaborators in the Laboratory have continued research on a variety of research topics all of which are related to an understanding of the physiology of the nervous system at the cellular level.

Dr. Lasansky has continued to examine structure-function relationships among elements in the retinas of tiger salamanders and snapping turtles. His work has revealed that the membrane response of rods and cones which occurs when light is directed at surrounding areas of retina is similar for both types of cells. He has hypothesized that the cone elements may mediate the observed response in rods through a synaptic form of interneuronal communication.

Dr. Wagner and collaborators have continued to analyze the spatial distribution of sensitivity in the vertebrate retina and to correlate this distribution with visual acuity, light adaptation and wavelength contrast enhancement. Dr. Wagner has also entered into collaboration with the Laboratory of Neuropathology and Neuroanatomical Sciences in order to study some of the pathophysiological changes in brain ischemia with electrophysiological recording techniques.

Dr. Smith and colleagues have studied certain aspects of electrically excitable membrane processes in ganglion neurons of Aplysia. They have found evidence to support their notion that Na^+ ions play a major charge-carrying role in pacemaker activity. They have also found that the cell body of ganglion cells in Aplysia is not the primary site of generation of action potentials, but rather acts in a relatively passive manner during spike generation. In another project they have developed and utilized a fluorescence microscope for examining Ca^{++} binding sites in cultured mammalian neurons. Their initial results indicate that these binding sites are localized to the cell bodies of sensory neurons.

Dr. Barker and colleagues have used electrophysiological recording techniques to study excitable membrane processes in cultured mammalian neurons and the actions of clinically important drugs. The principal observations from this year's research include the following: 1) one-half of the sensory neurons generate Ca^{++}-dependent K^+ conductances, probably by releasing Ca^{++} from intracellular stores; 2) a majority of spinal and hippocampal neurons possess a K^+ conductance which acts to regulate excitability; 3) a variable number of spinal and hippocampal neurons generate Ca^{++} conductances and Ca^{++}-dependent K^+ conductances; 4) 4-aminopyridine, a convulsant in vivo, produces paroxysmal episodes of excitatory activity and enhances transmitter release in culture by blocking the K^+ conductance described in 2) and promoting the Ca^{++}-dependent events described in 3); 5) a majority of spinal and hippocampal neurons generate a Na^+/K^+ conductance at relatively hyperpolarized levels of membrane potential; 6) all hippocampal neurons respond to GABA, muscimol and pentobarbital and the membrane response appears to be comprised of two-state ion channels whose properties are somewhat different from those found on spinal neurons; 7) neuroblastoma-glioma hybrid cells, which possess opiate receptors coupled to adenylate cyclase, respond to opiates and opioids with a novel type of increase in membrane conductance, possibly to Na^+ ions; 8) benzodiazepines and sub-anesthetic concentrations pentobarbital, but not phenobarbital, ethosuximide, or valproate potentiate membrane responses to GABA; 9) patch clamp recordings of GABA and muscimol-activated channels in cultured spinal neurons have confirmed the two-state nature of the events; 10) cholecystokin causes long-lasting excitatory effects in spinal neurons. The results from this research demonstrate that a variety of excitable membrane processes are present in mammalian CNS neurons. A primary goal will be to characterize how each excitable membrane process functions physiologically. Another related aim will be to show which forms of excitability are present in what types of mammalian central neurons.

The project, Neural Connections in the Retina: ZO1 NS 02152-08 LNP, has been terminated with the publication of the following paper: Amacrine Cells, Bipolar Cells, and Ganglion Cells of the Cat Retina. A Golgi Study, Helga Kolb, Ralph Nelson and Andrew Mariani. Vision Research 21: (1981) 1081-114.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02019 - 10 LNP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Electrophysiology and Neuropharmacology of Simple Cellular Systems
New title: Electrophysiological Studies on Neuronal Excitability

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.L. Barker	Laboratory Chief	LNP, NINCDS
	T.G. Smith	Section Chief	LNP, NINCDS
OTHER:	R. Canada	Staff Fellow	LNP, NINCDS
	E. Gratz	Staff Fellow	EB, NINCDS
	K. Futamachi	Staff Fellow	LNP, NINCDS
	M.A. Rogawski	PRAT Fellow	LNP, NINCDS
	R.E. Study	Staff Fellow	LNP, NINCDS
	D.A. Mathers	Visiting Fellow	LNP, NINCDS
	D.G. Owen	Visiting Fellow	LNP, NINCDS
	W. Vaughn	Computer Specialist	RSB, NIMH
	J. Mazzetta	Technician	LNP, NINCDS

COOPERATING UNITS (if any)
Research Services Branch, NIMH; R.N. McBurney, University of Newcastle-upon-Tyne Medical School, England; M. Segal, Weizmann Institute, Rehovot, Israel.

LAB/BRANCH
Laboratory of Neurophysiology

SECTION
Sections on Neurobiology and General Physiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6	4	2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experiments using intracellular and extracellular recording techniques have been carried out on various in vitro preparations of vertebrate and invertebrate neurons. The research has focussed primarily on characterizing the types of excitable membrane processes resident in neurons and secondarily on studying the effects of various transmitter substances and clinically important drugs on these processes. The principal conclusions are that multiple forms of electrically and chemically excitable conductance mechanisms are present in spinal, hippocampal, and hypothalamic nerve cells grown in tissue culture and that both endogenous transmitters and exogenous drugs alter these conductances in superficially similar ways. The results of this research improve our basic understanding of neuronal excitability and of the physiological roles of transmitters and the pharmacological actions of drugs.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02330 - 05 LNP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biochemical Pharmacology of Cultured Nerve Cells
New Title: Cellular Biological Studies of CNS Neurons

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.L. Barker	Laboratory Chief	LNP, NINCDS
OTHER:	M. Rogawski	PRAT Fellow	LNP, NINCDS
	A. Schaffner	Staff Fellow	LNP, NINCDS
	R. Study	Staff Fellow	LNP, NINCDS
	P. Sher	Staff Fellow	LDN, NICHD
	J. Mazzetta	Technician	LNP, NINCDS
	V. Smallwood	Technician	LNP, NINCDS

COOPERATING UNITS (if any)
LDN, NICHD: J. Neale, Department of Biology, Georgetown University; R. W. Olsen, University of California at Riverside; L. Skirboll, LCS, NIMH

LAB/BRANCH
Laboratory of Neurophysiology

SECTION
Section on Neurobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mouse spinal and sensory neurons grown in dissociated cell culture have been studied with various biochemical and immunohistochemical methods. The research has focussed on revealing the presence of specific membrane and cytoplasmic properties resident in cultured neurons. The principal observations from this year's research include: 1) the demonstration of glutamic acid decarboxylase activity in cultures of embryonic spinal neurons and its localization primarily to bouton-like structures investing cell bodies; 2) the demonstration of immunoreactivity to methionine- and leucine-enkephalin throughout the cytoplasm of 1-5 percent of spinal neurons; 3) the demonstration of immunoreactivity to dynorphin (1-13) at the level of the cell body in 1-5 percent of spinal neurons; 4) the demonstration by radioimmunoassay and immunohistochemistry of cholecystokinin and its receptors in sub-populations of cells; and 5) down-regulation of binding to benzodiazepines by chronic exposure to the drug.

4 LNP/IRP

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02339 - 05 LNP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Neural Coding and Processing of Information in the Visual System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H.G. Wagner	Section Chief	LNP, NINCDS
OTHER:	M.L. Wolbarsht	Professor	Duke Univ.
	E.F. MacNichol, Jr.	Director	Marine Biological Lab.
	M.A. Alli	Professor	University of Montreal
	G. David Lange	Associate Professor	Scripps Institute
	William Beane	Electronic Technician	LNP, NINCDS

COOPERATING UNITS (if any)
Ophthalmology Department, Duke University, Durham, N.C.; Marine Biological Laboratory, Woods Hole, Mass.; Biology Department, University of Montreal, Canada; Scripps Institute of Oceanography, Calif.

LAB/BRANCH
Laboratory of Neurophysiology

SECTION
Section on Neuronal Interactions

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.4	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We have continued our study of the receptive field of the retinal ganglion cells by analysing data collected on carp. We have found that the distribution profile of sensitivity across the field under either dark adapted or light adapted conditions can be described as gaussian. The gaussian shape suggests that the dendritic inputs to the ganglion cell would also show a gaussian distribution. Our examination of the morphological evidence indicates that this is not so. In addition, short duration stimuli were found to substantially broaden the quantitatively definable width for this receptive field.

Microspectrophotometric absorption curves for the outer segments of carp cones can be grouped into three classes which are identical to those observed in goldfish. Discrepancies which were present concerning the blue cone λmax have been resolved. Preliminary efforts to use these "class" curves as templates for the construction of spectral sensitivity curves in other fish such as the cichlids have met with some success.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 01659 - 14 LNP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Synaptic Contacts of Retinal Neurons

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. Lasansky	Research Biologist	LNP-NINCDS
	J. Lohr	Technician	LNP-NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Neurophysiology

SECTION
Section on Cell Biology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The responses of retinal rods of the turtle to annular illumination include a depolarizing component not seen when the center of the receptive field is also illuminated. While the latter feature indicates that the depolarization is of synaptic origin, it seems to exclude horizontal cell feedback as its source. Since the surround effect on rods can be seen under illumination bright enough to completely desensitize them, it must originate in the cone system and may reflect direct cone-rod interactions.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02152-08 LNP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Neural Connections in the Retina

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Henry G. Wagner	Chief	LNP, NINCDS
OTHER:	H. Kolb	Research Biologist	Univ. of Utah
	R. Nelson	Research Biologist	LVR, NEI
	A. Mariani	Research Biologist	LVR, NEI

COOPERATING UNITS (if any)
Dept. of Physiology, Univ. of Utah, Salt Lake City, Utah;
Laboratory of Vision Research, NEI.

LAB/BRANCH
Laboratory of Neurophysiology

SECTION
Section on Neuronal Interactions

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This research project was terminated in Fiscal Year 1981 with the publication of the paper cited below. The full citation of the published paper was not available at the time that the FY '81 report was submitted, and it is for that reason included in the FY '82 Annual Report.

Publication:

Kolb, H., Nelson, R., and Mariani, A.: Amacrine cells, bipolar cells and ganglion cells of the cat retina: A Golgi study. Vision Research 21:7, 1081 - 1114, 1981.

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Clinical Neurosciences Branch

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1981 through September 30, 1982
Clinical Neurosciences Branch
National Institute of Neurological and Communicative Disorders and Stroke

Paul Fedio, Ph.D., Acting Chief

Summary of Program Activity

The Clinical Neurosciences Branch (CNB) formulates and conducts basic and applied clinico-investigative research to advance an understanding of brain-behavior relations, applying electrophysiologic and neuropsychologic procedures to study altered neurologic conditions and events in man. These activities are supported by the equivalence of 6 man-years (1 professional, 3.5 technical and 1.5 secretarial staff members).

I. Clinical Diagnostic Services:

The principal clinical activities provide electroencephalographic (EEG) diagnostic services, including computer-derived, evoked potential studies of epilepsy, brain tumors, neuromuscular disorders and developmental metabolic anomalies. These consultative services are extended to the parent Institute NINCDS, and to other Institutes within NIH, and the sources of referral are listed as follows:

	Diagnostic Services			
Referral Sources	EEG	%	Evoked Potential	%
NINCDS	542	58.7	142	68.3
NIMH	117	12.7	2	0.9
NICHD	95	10.3	20	9.6
NHLBI	26	2.8	3	1.4
NCI	30	3.2	6	2.9
NIAID	44	4.8	8	3.9
NIADDK	37	4.0	12	5.8
NEI	8	0.8	1	0.5
MISC	25	2.7	14	6.7
TOTAL (1132)	924	100.0	208	100.0

The acturarial distribution reflects an increase in the total number of standard EEG referrals since the past year: 59% of patient referrals were submitted by NINCDS physicians, the remaining 41%, from other NIH sources. Services identified as miscellaneous represent bedside EEG recording performed in the CCU and electrocorticography (ECG) administered in the neurosurgical suite. Requests for the use of evoked potential studies have increased considerably during this period (visual, brainstem auditory and somatosensory potentials), a supplementary procedure which has proved especially useful in the diagnosis and management of demyelinating neurologic diseases.

The Branch also provides varied and suitable clinical opportunities and patient-study materials for clinicians who intend training in Clinical Electroencephalography. Each year, one or two of the Clinical Associate trainees become eligible for examination for the American Board of Qualification in EEG.

In addition to the EEG service, a team of neuropsychologists provides consultation to patients in NINCDS and other Institutes. Standard and specialized psychometric examinations are performed to provide diagnostic information, and to guide habilitative management of patients with neurologic and neuropsychiatric disorders. Special studies at preoperative and postoperative intervals have been developed to chart the course of neurosurgical treatments of patients with brain tumors and epilepsy.

II. Research Activities:

Branch members actively conducted seven (7) research projects during this reporting period, and in addition, engaged in secondary collaboration with other investigators within NINCDS and other Institutes.

Clinical seizure patterns elicited with different types of epilepsy continue to be a primary field of interest. Branch members have been using a standard EEG machine in tandem with Video recording instrumensts. This unique monitoring system allows the investigators to observe crucial ictal, clinical and EEG patterns simultaneously, which affords an opportunity to record observations and events for precise analysis. This system has greatly increased the reliability to correlate EEG parameters with specific seizure patterns, and to document rare electroclinical relations which occurred incidentally, during routine recordings with epileptic patients.

The branch staff has been heavily involved in a correlative study of "Electroencephalography (EEG), Computerized Axial Tomography (CAT), and Positron Emission Tomography (PET) with [^{18}F]2-Fluoro-2-Deoxyglucose (^{18}FDG)" in adults with gliomas. The relationship between EEG and static and dynamic radiographic parameters has been studied in 23 patients. PET scans showed cortical suppression in 14 of 16 patients and focal EEG slowing in 6 of 7 patients. Electrographic records show focal delta activity in 9 of 14 patients with tumors situated in both gray and white substance, and in 5 of 8 with tumors in white matter, verified only on CT scans. PET scans showed suppression of metabolic rate in areas adjacent to the tumor in 20 patients, including 6 of the 8 with tumors in white matter only. Fifteen (15) patients had focal EEG slowing, as did 2 of the 3 patients without cortical suppression. In 3 patients with rhythmic delta EEG activity, 2 had tumors which invaded the thalamus as documented by both the PET and CT scans. Four (4) patients had focal attenuation of the EEG background, and 3 of these also had thalamic involvement; none of the patients without background attenuation had thalamic involvement. Preliminary impressions suggest that focal EEG slowing cannot be directly related to involvement of white matter alone or to suppression of cortical metabolic activity. Rhythmic delta activity and suppression of EEG background, however, appear to be related to involvement of thalamic structures. Parenthetically, several patients with thalamic or subcortical involvement showed global cortical hypoactivity, inviting a proposal to study possible neuropsychological deficits.

In the collaboration with the Epilepsy Section, positron emission tomography with simultaneous EEG monitoring has been performed with 18-fluoro-2-deoxyglucose (FDG) in 10 patients with complex partial seizures; these patients presented normal CT profiles and neurological status at examination. Four (4) patients had unilateral epileptiform discharges, 2 had predominantly unilateral discharges, and 4 had bilateral epileptiform abnormalities. PET images were consistent with hypometabolic lesions in all patients except for 2 epileptic subjects with bilateral discharges. The PET scans were unaffected by the seizure frequency, state of alertness, or number of spike discharges. However, a change in antiepileptileptic medication between interictal scans has affected the imaged metabolic rate. Seizures occurring 18 and 90 minutes prior to FDG injection did not alter the hypometabolic area whereas seizures beginning 3 minutes after FDG injection in one patient (and occurring throughout FDG uptake in another) produced hypermetabolic uptake at the original interictal, hypometabolic focus. Part of the effect at 10 and 20 minutes in the former patient may have been due to increased cerebral blood flow. These data and impressions suggest that focal lesions may be detected by PET scan, even if the EEG abnormality is not well localized. Because PET provides reliable localization of focal abnormalities, this noninvasive procedure is especially significant in patients with medically intractable epilepsy, normal neurological and CT examinations, and who may be suitable surgical candidates.

An integrated effort is also being initiated to investigate the psychosocial and intellectual problems associated with epilepsy. Patients who have submitted to a unilateral left or right temporal lobe resection for the relief of intractable seizures, will serve as subjects. A series of studies, utilizing standard and specially designed tests of perception and memory, have been developed to assess reasoning and analytical defects, memonic disorders and the therapeutic effect of resection; the long term effects of brain surgery on cognitive and emotional behavior will be analyzed.

Emotional or affective changes experienced by patients with temporal lobe damage will also be addressed within the hypothesis that left and right brain mechanisms contribute differentially to emotional perception and regulation. The relationship between brain damage and ideative versus emotive changes will be examined with the intent of better understanding the nature of neuropsychiatric disorders in man and the role of defective neural mechanisms in regulating emotional behavior.

Apart from human experimentation, animal models will be used to extract data and information about epilepsy. Altered metabolic conditions and the relationship to seizure disorders will guide studies dealing with the effect of hypoxia or kindling in rats. Specifically, adult rats are exposed to nitrous oxide in an airtight chamber for a duration of 15 and 25 seconds, after which, the animals are allowed to recover for prescribed periods of time. Electrodes will then be implanted in the amygdala and over the cortical surface of brain. Awaiting their recovery for one more week, electrical stimulation for kindling will commence. So far, only a few rats have been prepared and subjected to the experiment, and a preliminary analysis does not show any significant difference in the rate of kindling between controls and hypoxic rats. This work will be amplified and include refinement of the experimental procedures. In order to assess the impact of hypoxia during early development of the CNS, newly born animals will be used.

CNB investigators have been also actively studying visual evoked potentials (VEP) in relationship to eye dominance. The results indicate that the amplitude of pattern-reversal VEPs in 25 healthy volunteers was significantly higher with stimulation of the dominant eye than the nondominant eye in subjects with preferred right eye sighting. The differences in VEP tracings were recorded over both cerebral hemispheres and midline leads; handedness did not appear to influence the amplitude asymmetry. A similar trend was noted for left eye dominant subjects, but the differences were significant only at an occipital reference (O_2). The mean latency of the P100 peak was significantly shorter with stimulation of the dominant eye. These amplitude and latency disparities between responses by dominant and nondominant eyes to stimulation provide additional electrophysiological evidence of lateralization in the nervous system.

To complement these studies which emphasize altered responsivity for early components in evoked potentials, new initiatives have been developed to examine the later waveform components (P300). This event-related brain potential has become established as a reliable index of the time and manner whereby information is processed. The P300 analysis will be utilized with various neurologic and neuropsychiatric patients, examining defects in memory, concept formation and the use of feedback to influence behavior, allowing the examiners to analyze the consequences of neurologic diseases in human behavior.

Apart from the electrophysiological techniques, a comprehensive neuropsychological study of human aging and alterations by dementia have been completed, describing and comparing cortical and subcortical dysfunctioning in patients with Alzheimer's and Huntington's Disorders. Preliminary impressions indicate that Alzheimer patients are troubled by pervasive or global intellectual decline. In most instances there appear to be no qualitative differences between demented and age-matched normal subjects. That is the patients did poorly in managing visual auditory, verbal and nonverbal memory tasks of a short or long term nature, and yielded a pattern of performance which was similar to that for normal individuals, but at a greatly reduced level of efficiency.

The initial analysis also shows that the memory impairment for Alzheimer's disease may result from 'poor encoding' of material presented to memory stores. This contrasts sharply with the basic flaw recorded for amnesic disorders where the deficit involves an inability to store and/or retrieve newly learned experiences or information.

Relatedly, Alzheimer patients exhibited selective neurolinguistic deficits, and did poorly with confrontation naming tasks. Their performance was characterized by a loss of knowledge about specific object attributes, while broad categorical information was relatively preserved. Coupled with spatial imperception, this defect disturbs the daily activities of demented patients, and to a lesser degree, in senesence, especially in novel, unfamiliar or unstructured personal-social situations, and may be cast as confusion and disorientation.

This pattern of functional flaws was not common to patients demented by Huntington's Disease. With visuospatial judgmental and constructional tasks, Huntington patients did poorly with 'egocentric'tasks, that is, manipulation of one's own body (internal) in space. In contrast, Alzheimer patients were more troubled in handling 'allocentric' tasks, that is, manipulation of objects in external space. These findings are interpreted within the framework of frontal versus parietal lesions respectively, implicating distinct structurofunctional differences between Alzheimer's and Huntington's disorders.

A statistical, discriminant analysis is currently being executed to evaluate the notion that dementia of the Alzheimer's variety does evolve in a uniform manner, that various subgroups exist, with salient and progressive weaknesses in language, attention or constructional deficits, reflecting differential brain changes.

Relatedly, parallel neuropsychological efforts were extended to Guam where a high incidence of Parkinson Dementia prevails among members of the indigenous Chamorros race. The research findings indicate that Parkinson Dementia (Guam) and Alzheimer's Disorder (U.S.) produced functionally similar deficits in comparison with matched normal subjects. Defects were recorded on measures of attention, memory, visual spatial construction, and language. The resultant differences however, were noteworthy: with auditory-language dependent tasks, the Guamanian patients did more poorly than Alzheimer patients, whereas, with visual memory tasks, the Alzheimer patients were inferior to the Parkinson-demented subjects on Guam. These data underscore that mental deterioration following diffuse brain changes, are tempted by native cognitive styles, and that functional organization of brain mechanisms is shaped by environmental and genetic determinants.

Specialized study of neuropsychiatric disorders involved patients with obsessive-compulsive ideation and mannerisms, addressing hypothetical impressions about disturbances to frontal-structural systems. In collaboration with NIMH scientists, adolescents and adults with obsessive-compulsive features were studied by specialized procedures. The findings established selective defects with spatial procedures involving perception, memory and learning. The patients tended to ignore prescribed test constraints and shifted prematurely from one learned concept to another. The data implicate altered functions dependent on frontal lobe integrity and invite conjecture of possible overexcitation of frontal limbic mechanisms in obsessive-compulsive disorders.

In collaboration with medical specialists and scientists in NINCDS and NIMH, developmental irregularities of metabolic disorders and the early effects of radiation of the brain are being examined. In one study, neuropsychological sequelae were examined in pediatric patients receiving prophylactic CNS treatments for acute Lymphoblastic Leukemia. Radiographic study of these patients illustrated dilation of the ventricles and subarachnoid spaces, and evidence of calcification in the basal ganglia. In behavioral terms, these changes were related to major deficits in attention, memory and learning, and diminished intellectual competence.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 00200-28 CN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Cognitive and Emotional Profile of Neuropsychiatric Disorders.
Former Title: Involuntary Movements

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Fedio	Psychologist	CN	NINCDS
	A. Martin	Psychologist	CN	NINCDS
	P. Brouwers	Psychologist	CN	NINCDS
OTHER:	C. Cox	Psychologist	CN	NINCDS
	J. Bravo	Psychologist	CN	NINCDS
	T. Chase	Neurologist	ET	NINCDS

COOPERATING UNITS (if any)
Experimental Therapeutics Branch, NINCDS

LAB/BRANCH
Clinical Neurosciences

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.7	1.2	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

x

A neuropsychological profile of dementia was drafted for individuals with Alzheimer's Disease, Huntington's Disease and 'at risk' for Huntington's Disease. The evaluations extended into memory, learning and perceptual areas, utilizing standard and experimental tasks, also establishing normative references for functional changes encouraged by the aging processes. These behavioral data will be collated with biochemical and neuroradiometric measures, and independent indicators of deterioration and dementia will be developed. In collaboration with NINCDS facilities on Guam, the investigation will attempt to study Parkinsonian Dementia among the indigenous population and compare data with results obtained from demented patients in the U.S.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01245-17 CN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

EEG Learning Correlates Using Scalp and Intracranial Depth Electrodes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Fedio	Psychologist	CN	NINCDS
	R. Johnson	Psychologist	CN	NINCDS
OTHER:	M. Buchsbaum	Research Medical Officer	BPB	NIMH
	A. Martin	Psychologist	CN	NINCDS
	P. Brouwers	Psychologist	CN	NINCDS

COOPERATING UNITS (if any)

Biological Psychiatry Branch, NIMH

LAB/BRANCH
Clinical Neurosciences

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Information processing by the human brain was monitored and quantified by averaged evoked response techniques. The electrographic activity was recorded from left and right brain regions during memory and perception in normal subjects, and in patients with neuropsychiatric disorders (Alzheimer's). Suspect electroencephalographic disturbances in brain-behavior relations in psychiatric patients was also evaluated, relating left brain dysfunction to ideational disorders, and right brain activity to maladaptive emotional reactions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 01424-16 CN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Response Modulation by the Limbic System in Man: Neuropsychological and Physiological Changes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Fedio	Psychologist	CN	NINCDS
	A. Martin	Psychologist	CN	NINCDS
	P. Brouwers	Psychologist	CN	NINCDS
OTHER:	C. Cox	Psychologist	CN	NINCDS
	J. Bravo	Psychologist	CN	NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Clinical Neurosciences

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	0.6	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Emotional and cognitive characteristics are studied in epileptic patients with unilateral left or right temporal lobe injury. Temporal epileptic patients are compared with matched normal subjects and patients with other neurologic disorders. The epileptic patients judge and learn information conveying different emotional states, while behavioral and physiological events are recorded. The research examines the role of the temporal lobe in establishing specific limbic associations between the left and right hemispheres in regulating cognitive functions and emotional experiences in man.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01658-15 CN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hemispheric Development and Specialization of the Intellectual Functions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Fedio	Psychologist	CN	NINCDS
OTHER:	A. Martin	Psychologist	CN	NINCDS
	P. Brouwers	Psychologist	CN	NINCDS
	C. Cox	Psychologist	CN	NINCDS
	C. Kufta	Medical Officer	SN	NINCDS

COOPERATING UNITS (if any)

Surgical Neurology Branch, NINCDS

LAB/BRANCH

Clinical Neurosciences

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	0.6	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The disabling effects of cerebral insult were evaluated by a broad range of neuropsychological tests evaluating brain-behavior in man. Changes in the intellectual behavior of neurologically-impaired individuals were evaluated before and after surgery, during electrical stimulation of the brain with specialized CNS procedures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02269-06 CN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Visual Evoked Potentials in Clinical Neurology and Neuro-Ophthalmology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. Sato, M. D.	Medical Officer	EB	NINCDS
OTHER:	J. Chassy	EEG Technologist	CN	NINCDS

COOPERATING UNITS (if any)

Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH

Clinical Neurosciences, IRP

SECTION

Clinical Neurophysiology

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An analysis of the morphology, amplitude and latency of visual evoked potentials to photic flashes and reversing checkerboard pattern is being conducted. Normative data have been collected from normal individuals, predominantly of 20-39 years. Visual evoked responses also have been examined in patients with various neurological disorders. Prolonged latencies of the major positive peak have been noted in patients with multiple sclerosis and neurological disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02431-03 CN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Experimental Epilepsy: Seizures Produced by Kindling in Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. Sato, M.D.	Medical Officer	EB	NINCDS
OTHER:	S. Walbridge	Laboratory Specialist	CN	NINCDS

COOPERATING UNITS (if any)
Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH
Clinical Neurosciences, IRP

SECTION
Clinical Neurophysiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.6	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Seizures produced by chronic stimulation (Kindling) are a good model for human epilepsy. In rat, seizures are produced by daily electrical stimulation of amygdaloid complex and other central nervous system sites. In this project, Kindling of the various sites of the central nervous system, interictal epileptiform discharges and their propagation, and effects of sleep-wake cycles and maturation on the epileptiform discharges are being investigated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02432-03 CN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Brainstem Auditory Evoked Potentials in Clinical Neurology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. Sato, M. D.	Medical Officer	ETB	NINCDS
OTHER:	J. Chassy	EEG Technologist	CNB	NINCDS

COOPERATING UNITS (if any)

Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH

Clinical Neurosciences, IRP

SECTION

Clinical Neurophysiology

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analysis of the morphology, amplitude and latency of brainstem auditory evoked responses to clicks is being conducted. Normative data have been collected from normal subjects, predominantly of 20-29 years. The test has been carried out in patients with various neurological disorders. Prolonged latencies and distortion of morphology have been observed in patients with Multiple Sclerosis and Spinocerebellar Degeneration. The effect of pharmacological agents on the evoked responses is also being studied.

ANNUAL REPORT

October 1, 1981 through September 30, 1982
Developmental and Metabolic Neurology Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1981 through September 30, 1982
Developmental and Metabolic Neurology Branch
National Institute of Neurological and Communicative Disorders and Stroke
Roscoe O. Brady, Chief

The principal activities of the Branch concern the following areas of investigation: 1. Metabolism of complex lipids and mucopolysaccharides in normal and pathologic states. 2. Enzyme replacement therapy for the treatment of patients with hereditary metabolic disorders. 3. Transmembrane signalling mechanisms and the role of glycolipids and glycoproteins in this process. 4. The involvement of glycoproteins of the myelin sheath in nervous system development and in demyelinating diseases. 5. The role of cell surface enzymes in cellular communication and in affective disorders. 6. Development of non-sensitizing enzymes for the treatment of thromboembolic diseases. 7. Preparation of enzymes that degrade neurotoxic substances.

I. HEREDITARY METABOLIC DISORDERS

A. Molecular genetics of Gaucher's disease.

We have developed a large-scale high pressure liquid chromatography procedure for the preparation of homogeneous human placental glucocerebrosidase. This innovation has permitted us to determine the precise molecular weight and characteristics of the enzyme, its carbohydrate content, and the ability to raise polyclonal and monoclonal antibodies to this protein. Using these antibodies, we have demonstrated the nature of the discrete allelic modifications of glucocerebrosidase in non-neuronal (Type 1) and the neuronal (Types 2 and 3) forms of Gaucher's disease.

B. Excretion of Sphingolipids Via the Bile.

During the past year we discovered that comparatively large quantities of sphingolipids, such as glucocerebroside that accumulates in patients with Gaucher's disease, are excreted in the bile. This observation is consistent with an earlier finding that only a small percent of the daily turnover of glucocerebroside actually accumulates in patients with this disorder. This discovery has important implications for the development of alternative therapeutic strategies such as attempting to increase the excretion of accumulating sphingolipids by agents that stimulate the flow of bile.

C. Development of Animal Models of Human Hereditary Disorders.

The cyanohydrin derivative of glucocerebroside was synthesized. It is expected that this cyanogenic substance will enable us to select mutated cells that are deficient in glucocerebrosidase in order to develop a true genetic counterpart of Gaucher's disease in rodents. We have continued studies with the suramin-induced model of mucopolysaccharide storage disorders discovered by our Branch. Specific enzyme alterations have been demonstrated that explain the accumulation of these substances as well as gangliosides that occur

in excess in the brain of these animals and in patients with disorders of this type. Current research deals with attempts to understand the pathogenesis of the organomegaly in these animals and in patients with mucopolysaccharide storage diseases. In addition, we are participating in a study with investigators in NIADDK with a recently discovered canine model of Hurler's disease that should be useful for numerous investigations concerning this metabolic disorder and for comprehensive examinations of various therapeutic strategies.

II. ENZYME REPLACEMENT THERAPY FOR LIPID STORAGE DISEASES

A. Enzyme Replacement Trials in Gaucher's Disease

We have continued our investigation of enzyme replacement therapy in young patients with Type 1 (non-neuronal) Gaucher's disease. We continue to gratified by their clinical response and we are now in the control (third) stage of this investigation. We have carried out experiments to secure specific data concerning platelet sequestration and survival in these patients. The initial results indicate that platelet recovery and survival is vastly improved in Gaucher patients after enzyme replacement.

B. Specific Targeting of Exogenous Enzymes

We have demonstrated that the addition of linear pentamannoside chains to native human placental glucocerebrosidase causes little improvement in the delivery of the enzyme to the storage (Kupffer) cells in the liver. However, covalent linkage of triantennary molecules of trimannosyldilysine to the enzyme significantly increases the delivery of this enzyme by selective removel of hexoses provides even greater delivery of the enzyme to cells of the monocyte-macrophage system and we plan to employ enzyme modified in this fashion in clinical trials.

C. Delivery of Enzymes to the Central Nervous System

A major development in the past year was the conclusion of an agreement with investigators at the University of Alabama in Birmingham to collaborate in enzyme replacement trials in cats with the metabolic disorder known as generalized (G_{M1}) gangliosidosis. We shall provide purified β-galactosidase for this effort and we shall measure the effect of this exogenous enzyme on the quantity of stored ganglioside in the brain of the animals after appropriate temporary alteration of the blood-brain barrier. This is an immensely important step forward since we should be able to decide with this model whether enzyme replacement can reduce the quantity of accumulating lipid in the neurons in the brain of humans. If successful, this demonstration will provide a sound basis for enzyme replacement trials in human metabolic disorders that involve the central nervous system.

III. MEMBRANE RECEPTORS FOR ENVIRONMENTAL SIGNALS

The ganglioside G_{M1} can function as receptor for both cholera toxin and for the heat-labile toxin of *E. coli* which activate the enzyme adenylate cyclase to increase intracellular cyclic AMP (the "second messenger system") through ADP-ribosylation of a component of this enzyme complex. Gangliosides are synthesized within the cell and then transported to the plasma membrane. This transport is temperature-dependent but not affected by inhibitors of protein synthesis, agents that alter the cytoskeleton or energy metabolism. Glucocerebroside is synthesized in the rough endoplasmic reticulum and other sugars are added in the Golgi apparatus in cells. Various drugs including the ionophore monensin, block the conversion of glucocerebroside to higher sphingolipid homologues such as gangliosides by preventing the transport of glucocerebroside to the Golgi apparatus.

Critical studies have advanced our knowledge concerning the coupling of receptors on cell surfaces to the various components of the adenylate cyclase system. Many cells lose their responsiveness to hormones upon exposure to these agents (downregulation). This process appears to occur by the following sequence of events. First, the receptor is uncoupled from adenylate cyclase; second the receptor and its bound hormone are internalized; and third the hormone and receptor are degraded intracellularly.

IV. MULTIPLE SCLEROSIS

Information on the processing and metabolism of the specific myelin-associated glycoprotein (MAG) has accumulated rapidly in FY-82. It has been found that this myelin component is selectively localized in the periaxonal region of the myelin sheaths in the central and peripheral nervous system where it is likely involved in glia-axon interaction. We have demonstrated a proteolytic enzyme which is maximally active at neutral pH, is present in myelin and catalyzes the degradation of MAG to a smaller derivative (dMAG). The activity of this enzyme is considerably greater in periplaque areas in the brains of patients with multiple sclerosis than in comparable regions of normal brain. The dMAG that is produced by this enzyme is much more easily solubilized from myelin than is the parent compound. It is therefore likely that in multiple sclerosis, MAG is partially degraded and it becomes dislocated from its natural periaxonal location. These events lead to disruption of the normal glia-axonal relationship and initiate the breakdown of myelin.

Another important discovery during FY-82 was the demonstration that MAG is the peripheral nerve antigen that reacts with monoclonal IgM antibodies in a number of cases with plasma cell dyscrasias that are associated with peripheral neuropathy. Elucidation of the pathogenetic mechanism of this phenomenon should provide cnsiderable insight into the role of MAG in autoimmune diseases of the nervous system.

V. ECTO-ENZYMES

Important progress was made in FY 82 concerning the role and function of enzymes on the surfaces of cells (ecto-enzymes). It was discovered that there is an important feed-back system that recognizes when there is a requirement for these enzymes as they are depleted by exfoliation in the form of micro-

vesicles (exosomes) from cultured brain cells. The precise role of these enzymes in intercellular communication remains to be determined.

Studies on calcium-activated ATPase, a similar enzyme on the surface of erythrocytes, provided the following extraordinarily interesting observation. In a comparison of the activity of this enzyme in red blood cells from normal individuals and from manic-depressive patients, it was found that the activity of this enzyme varied much more in patients with bipolar affective disorders than in the control population. These wide fluctuations appear to be caused by alterations in the level and interaction of modulating factors such as calmodulin that bind to erythrocyte membranes and radically alter their biological properties including the activity of this ATPase. If this observation is substantiated in independent studies, it will provide an important handle for the investigation of the pathogenesis of human effective disorders.

VI. TREATMENT OF STROKES WITH CLOT-LYSING ENZYMES

The bacterial enzyme streptokinase is being used with increasing frequency to dissolve fibrin clots in the treatment of strokes and acute myocardial infarctions. A principal limitation of this approach is that the bacterial enzyme elicits a strong antibody reaction in recipients which severely reduces its effectiveness on repeated administration. In an attempt to circumvent this difficulty, we prepared high molecular weight polyethylene glycol adducts of streptokinase and examined their antigenicity and thrombolytic effectiveness. The adducts were much less antigenic than the unmodified enzyme and they retained full activity with chromogenic peptides commonly used to assay amidolytic activity. However, the adducts demonstrated marked reduction in fibrin clot lysis. Antigenicity and thrombolytic capacity will be examined using adducts prepared with lower molecular weight polyethylene glycol congeners.

VII. ENZYMES THAT DEGRADE NEUROTOXIC SUBSTANCES

In collaboration with investigators in NHLBI, an enzyme that degrades barbital has been isolated for the first time from a soil microorganism. The characteristics and requirements of this enzyme are being determined and its effectiveness in counteracting lethal doses of barbiturates will be examined in experimental animals. If this approach to the treatment of neurotoxins is successful, we shall try to develop enzymes that degrade other toxic substances and we shall attempt to render them non-antigenic with polyethylene glycol adducts as indicated in Section VI.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: NEW ENGLAND ENZYME CENTER, TUFTS UNIVERSITY (NO1-NS-0-2339)

Title: Preparation of Ceramidetrihexosidase from Human Placental Tissue

Contractor's Project Director: Henry E. Blair

Current Annual Level of Support: $80,933

Objectives: To isolate human placental ceramidetrihexosidase in sufficient quantity and purity so that it can be used in enzyme replacement trials in patients with Fabry's disease.

Major Findings: A procedure is being developed for the large-scale isolation of human placental ceramidetrihexosidase of sufficient purity and catalytic activity so that it can be safely administered to patients with Fabry's disease. Previous replacement trials with small quantities of this enzyme indicated that it catalyzed the clearance of accumulated lipid but that much larger quantities of the enzyme would be required in order to expect a beneficial clinical response. The necessary trials have been delayed by the presence of pyrogenic material(s) in larger batches of the enzyme. During the past year satisfactory progress has been made by the contractor in eliminating this this contaminant and it is anticipated that further clinical trials will soon be possible.

Significance to Biomedical Research and to the Program of the Institute: A principal mission of the Institute is to develop effective procedures for the treatment of human diseases. If the early encouraging results with small quantities of enzyme can be extended and enlarged, it is expected that this form of treatment will be useful for Fabry's patients.

Proposed Course of the Contract: We expect that adequate quantities of pyrogen-free ceramidetrihexosidase will be made available by the contractor for clinical trials. If the results that are obtained are sufficiently promising, a sufficient number of patients will be examined so that a reliable decision can be made concerning the effectiveness of enzyme replacement therapy in Fabry's disease.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: WEIZMANN INSTITUTE OF SCIENCE (NO1-NS-0-2333)

Title: Production of Three Radiolabeled Glycolipid Substances

Contractor's Project Director: David Shapiro, Ph.D.

Current Annual Level of Support: $56,000

Objectives: The enzymatic defects in heritable sphingolipid storage disorders in humans is ultimately best diagnosed through the use of radioactively labeled natural lipid substrates. The Weizmann Institute of Science provides the NIH with radioactive carbon-^{14} labeled glucocerebroside, sphingomyelin, and ceramidetrihexoside for the diagnosis of patients and detection of carriers of Gaucher's disease, Niemann-Pick disease, and Fabry's disease respectively.

Major Findings: The principal investigator is a world-recognized expert in the chemical synthesis of sphingolipids. He has devised procedures for incorporating radioactive carbon-^{14} into critical portions of sphingolipid molecules. Using these substrates, we incubate human tissue specimens to determine the activity of glucocerebrosidase, sphingomyelinase, and ceramidetrihexosidase enzymes. These determinations permit us to diagnose patients with the disorders listed above, to identify heterozygous carriers of these metabolic diseases, and to monitor pregnancies at risk for any of these conditions. These labeled lipids are also required to monitor the enzymes for therapeutic replacement trials. During the past year, the project director completed the synthesis of the first syanohydrin derivative of a sphingolipid. This analogue will be used in an attempt to develop rodent model of Gaucher's disease.

Significance to Biomedical Research and to the Program of the Institute: The ability to diagnose patients, identify heterozygotes, and monitor pregnancies at risk for any of the known lipid storage diseases represents major contributions to the control of the incidence of the sphingolipidoses at the present time.

Proposed Course of the Contract: The contractor will provide necessary radioactive sphingolipids for diagnostic tests and enzyme purification procedures. He will develop additional sphingolipid analogues for the production of animal models of human lipid storage diseases and he will prepare specific ligands for the purification of various sphingolipid hydrolases by affinity column chromatography.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1981 through September 30, 1982

Contractor: NEW ENGLAND ENZYME CENTER, TUFTS UNIVERSITY (NO1-NS-5-2321)

Title: Preparation of Glucocerebrosidase from Human Placental Tissue

Contractor's Project Director: Henry E. Blair

Current Annual Level of Support: $300,000

Objectives: To isolate human placental glucocerebrosidase in sufficient quantity and purity so tht it can be used in enzyme replacement trials in patients with Gaucher's disease.

Major Findings: A procedure has been developed for the large-scale purification of human placental glucocerebrosidase that is of sufficient purity and catalytic activity that it can safely be administered to humans with Gaucher's disease. The intravenous infusion of this enzyme to 12 patients with this disorder has brought about the following effects: (1) The progressive enlargement of the spleen and liver of these patients has been arrested. (2) The blood platelet count has been stabilized. (3) The general health and vigor of the recipients has dramatically improved.

Significance to Biomedical Research and to the Program of the Institute: One of the principal missions of the Institute is to develop effective therapy for the treatment of human diseases. If the results obtained in the initial trials of prospective enzyme replacement therapy discussed in the preceding paragraph can be extended and confirmed, we will have accomplished an unprecedented feat.

Proposed Course of the Contract: We have entered the control (third phase) of this investigation. Recipients have been randomized, some receiving the enzyme and others only the vehicle used to stabilize the enzyme preparation. We are also seeking to modify the enzyme so that it is more efficiently delivered to the specific cells that store the accumulating lipid. Finally, we shall investigate the possibility of altering the bloodbrain barrier to try to deliver the enzyme to the central nervous system in patients with the neuronopathic form of this disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 00706-23 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Inborn Errors of Metabolism of Diverse Etiology.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John A. Barranger, M.D., Ph.D.	Chief, Clinical Investigations and Therapeutics Section	DMN	NINCDS
Other:	George Constantopoulos, Ph.D.	Research Biochemist	DMN	NINCDS
	Daniel W. Stowens, M.D.	Clinical Associate	DMN	NINCDS
	Edward I. Ginns, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Norman Barton, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Shutish C. Patel, M.D.	Medical Staff Fellow	DMN	NINCDS
	Roscoe O. Brady, M.D.	Chief	DMN	NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.8	1.7	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) A better understanding of metabolic disorders which affect the nervous system is the goal of this project. In some phases, the studies are purely diagnostic and area applied to assist in identifying the less common disorders of metabolism. Other phases deal with biochemical observations in known disorders that suggest steps in the pathogenesis of the disease. In some poorly understood groups of neurologic disease, studies are conducted to draw biochemical correlations where none had previously been known or were poorly developed. Therapeutic trials are conducted in selected disorders. A new phenotype of glycerol kinase deficiency has been identified. Pyruvate dehydrogenase complex has been examined in subjects with spinocerebellar degenerations. Contrary to published reports, no deficiency of this enzyme has been established in any case. Work has begun to examine other oxidative enzymes in these diseases. In addition, hexosaminidase has been measured in these patients and found to be normal in all cases. Neurotransmitter alterations have been suggested by the clinical status of this group and study of their neurotransmitter concentrations and metabolites has begun.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 00815-22 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Metabolism of Complex Lipids of Nervous Tissue

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. O. Brady, Chief	DMN	NINCDS
OTHER:	P. G. Pentchev, Biochemist	DMN	NINCDS
	A. E. Gal, Organic Chemist	DMN	NINCDS
	J. A. Barranger, Section Chief	DMN	NINCDS
	A. D. Boothe, Veterinary Pathologist	DMN	NINCDS
	H. Weintraub, Visiting Fellow	DMN	NINCDS
	N. Sakuragawa, Guest Worker	DMN	NINCDS
	T. Neff, Chemist	DMN	NINCDS

COOPERATING UNITS (if any)

Weizmann Institute of Science, Rehovot, Israel
Tufts University Medical School, Boston, Massachusetts
National Center for Nervous, Mental and Muscular Disorders, Tokyo, Japan

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Enzymology and Genetics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7.6	6.6	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

1. Significant excretion of glucocerebroside via the bile in patients with Gaucher's disease has been demonstrated. This observation is consistent with our previous finding that only a small portion of the daily turnover of glucocerebroside accumulates and contributes to the pathogenesis of Gaucher's disease. We propose to investigate how this excretory pathway might be augmented in order to reduce the accumulation of lipid in this hereditary metabolic disorder. 2. The chemical synthesis of the cyanohydrin derivative of glucocerebroside has been accomplished. We intend to use this compound to select for mutant cells deficient in glucocerebrosidase to develop an animal model of Gaucher's disease. 3. We have demonstrated the catabolism of accumulated sphingomyelin by exogenous sphingomyelinase in tissue specimens from our animal model of human Type C Niemann-Pick disease and we have improved our procedure for the isolation of sphingomyelinase from human placental tissue in order to pursue enzyme replacement in Niemann-Pick disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01309-17-DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biosynthesis and Function of Glycosphingolipids and Other Glycoconjugates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. H. Fishman, Ph.D., Section Chief	DMN	NINCDS
OTHER:	H. Miller-Podraza, Ph.D., Visiting Fellow	DMN	NINCDS
	R. V. Rebois, Ph.D., Staff Fellow	DMN	NINCDS
	R. O. Brady, M.D., Branch Chief	DMN	NINCDS

COOPERATING UNITS (if any)
Laboratory of Cellular Metabolism, NHLBI

LAB/BRANCH
Developmental & Metabolic Neurology Branch

SECTION
Membrane Biochemistry

INSTITUTE AND LOCATION
NINCDS, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.6	2.0	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) 1. The ganglioside GM_1, the receptor for cholera toxin (CT), can also function as a receptor for E. coli heat-labile enterotoxin. Thus, these two pathogenic toxins, which activate intestinal mucosal adenylate cyclase by the same mechanism of ADP-ribosylation, appear to utilize the same receptor. 2. Although gangliosides function as receptors for bacterial toxins, they are not involved in the binding and action of glycopeptide hormones such as LH and hCG. Murine Leydig tumor cells contain gangliosides and bind and respond to hCG and CT. Using various techniques, GM_1 was shown to be the CT receptor in these cells whereas the hCG receptor was found to be a glycoprotein. In addition, gangliosides were not required for hormone action. 3. Gangliosides are synthesized inside the cell and then transported to the plasma membrane. Transport istemperature dependent but not blocked by inhibitors of protein synthesis, cyto - skeletal assembly or energy metabolism. Synthesis appears to occur at two separate sites. Glucosylceramide is formed to the rough endoplasmic reticulum whereas further glycosylation occurs in the Golgi apparatus. Several drugs including monensin, an ionophore, block the conversion of glucosylceramide to more complex glycolipids by preventing its transport to the second glycosylation site in the Golgi.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 01457-16 DMN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Chemical Synthesis of Radioactive Sphingolipids

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A. E. Gal, Chief, Neurochemical Methodology Section DMN, NINCDS
OTHER: F. J. Fash, Bio. Lab. Technician DMN, NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Neurochemical Methodology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) In the framework of this project. Spingolipids containing radioactive isotopes were synthesized and used for metabolic studies and as diagnostic tools in sphingolipidoses. ^{14}C and ^{3}H labels were introduced by synthetic and semi-synthetic techniques, gas exposure, and a new approach: functional group exchange. These techniques were used for the syntheses of radioactive enantiomorphic derivatives of sphingolipids. These products are not metabolizable. Experimentation with these in animals creates "animal models" for metabolic diseases and opens new areas for biomedical studies.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-01480-15 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Metabolism of Neurohumoral Substances in Marine Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. G. Trams, Chief, Physiology and Metabolism Section,	DMN, NINCDS
OTHER:	N. Salem, Senior Staff Fellow	DMN, NINCDS
	C. Lauter, Chemist	DMN, NINCDS
	J. Doherty, Toxicology Branch, EPA	

COOPERATING UNITS (if any)
Mote Marine Lab., Sarasota, Florida
Hazard Evaluation Division, Environmental Protection Agency, Washington, D.C.

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Physiology and Metabolism

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to explore the great variety and abundance of the marine environment for molecular models of neurobiology. In particular it was designed to investigate species or phenomena which display an amplification or simplification of human physiologic or pathologic metabolism. Further studies were conducted on the neurotoxic effects of several pesticides in tissue preparations derived from lobster axons and from mammalian brains. Pyrethroid markedly inhibit calcium and dopamine uptake in rat brain nerve ending preparations and in lobster plasma membranes. Comparative studies of brain nucleotide and ecto-enzyme levels in elasmobranch, teleost, reptile, and avian species demonstrated remarkably similar nucleotide profiles but widely differing phosphoesterhydrolase activities.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01481-15 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Studies on the Composition and Metabolism of Cellular Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. G. Trams, Chief, Physiology and Metabolism Section DMN,NINCDS
OTHER: N. Salem, Senior Fellow DMN,NINCDS
C. Lauter, Chemist DMN,NINCDS
E. MacDonald, Visiting Fellow DMN,NINCDS
S. Patton, Professor, University of California

COOPERATING UNITS (if any)
Dept. of Neurosciences, University of California, San Diego, CA.

LAB/BRANCH
Developmental & Metabolic Neurology Branch

SECTION
Physiology and Metabolism

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.3	3.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) The objective of this project is to elucidate the relationship between molecular composition and topographic arrangements of membrane building blocks with reference to plasma membrane function. Bioelectrogenesis, transport and many metabolic phenomena are based on the proper associations of membrane proteins and lipids. Membrane ecto-enzymes are glycoproteins and require a lipophilic environment for optimal activity. Ecto-phosphoesterhydrolases appear to be a part of a regulatory system which modulates membrane permeability and excitability. We have challenged this system by inactivation of ecto-5-nucleotidase with membrane impermeable modifiers such as Concanavalin A or trinitrobenzenesulfonic acid. Cultured brain cells respond by replacing the surface enzyme and decreasing exfoliation of activity in the form of microvesicles (exosomes). This response appears to be the result of recognition of decreased ecto-5'-nucleotidase activity and a selective conservation of the enzyme in the exfoliative process. Studies of ATPases in human erythrocyte membranes of normal and manic-depressive populations suggest that the variations found in patients with bipolar effective disorders is caused by periodic fluctuations in levels of factor(s) which bind to erthrocyte membranes and radically alter their biological properties.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01808-13 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Glycoproteins of Myelin in Development and Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. H. Quarles, Chief, Myelin and Brain Development Section, DMN, NINCDS

OTHER: R. O. Brady, Chief, DMN, NINCDS
D. Johnson, Visiting Fellow, DMN, NINCDS
T. Inuzuka, Visiting Fellow, DMN, NINCDS

COOPERATING UNITS (if any)
Cellular Neuropathology Section, LNNS, NINCDS
Electron Microscopy Section, ID, NINCDS

LAB/BRANCH
Developmental and Metabolic Neurology Branch, NINCDS

SECTION
Myelin and Brain Development

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.1	3.1	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) The myelin-associated glycoprotein (MAG) is selectively localized in the periaxonal part of CNS and PNS myelin sheaths where it is likely to be involved in glia-axon interactions. In the PNS, it is also present in the outer mesaxon, Schmidt-Lanterman incisures, and the lateral loops. It is hypothesized that the bulky MAG molecule is responsible for the greater separation of the Schwann cell membranes in these locations than in the compact myelin. During peripheral nerve myelination, MAG increases slightly before the major PO glycoprotein increase. MAG has been identified as the myelin antigen that reacts with monoclonal IgM in a number of patients with peripheral neuropathy associated with paraproteinemia. Metabolic studies in developing rat brain have demonstrated membrane fractions that contain MAG of very high specific radioactivity and which may be precursors of compact myelin. There is a neutral protease in myelin purified from human brain which rapidly converts MAG to a slightly smaller derivative (dMAG). This proteolytic activity is significantly greater in myelin isolated from multiple sclerosis brain than in myelin from control brain.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02162-08 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Synthesis of Compounds Analogous to Glycolipids

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A. E. Gal, Chief, Sect. on Neurochem. Methodol. DMN, NINCDS
OTHER: F. J. Fash, Bio. Lab. Technician DMN, NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Neurochemical Methodology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Conduritol β-epoxide, a saccharide that strongly inhibits β-glucosidases, was synthesized by a method developed by this section that provides the product in greater yield than previously available and permits the preparation of this compound containing a tracer with extraordinarily high specific radioactivity. Administration of conduritol β-epoxide to animals produces a syndrome that resembles Gaucher's disease in humans by inhibiting the enzyme glucocerebrosidase. Radioactive conduritol β-epoxide reacts with the active site of glucocerebrosidase isolated from normal human tissues and from patients with Gaucher's disease. This use of the radioactive conduritol β-epoxide will materially accelerate the identification of the amino acid substitutions (or deletions) that occur in the glucocerebrosidase molecule in patients with Gaucher's disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02163-08 DMN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Special Analytical Methods and Preparative Techniques to Investigate the Etiology and Therapy of the Sphingolipidoses

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A. E. Gal, Chief, Neurochemical Methodology Section DMN NINCDS

OTHER: F. J. Fash, Biol. Lab. Technician DMN NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Neurochemical Methodology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS XX(b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

New analytical techniques were developed and used in enzymatic research and in clinical investigations of lipidoses. The lipid content in human tissues, the diagnosis of lipid storage diseases by gas, thin-layer chromatography and other techniques were studied at the microgram level. The techniques we developed previously were improved, modified and used in connection with ongoing projects related to lipidoses in our laboratories and also as joint projects with outside groups. Numerous analytical studies were undertaken by using these techniques. Complex lipids were determined in pericardium, in human glionic cell lines, erythrocyte lipids and in tissues from patients with lipofuscinosis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02366-04 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Regulation of Hormone-Responsive Adenylate Cyclase

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. H. Fishman, Ph.D., Section Chief	DMN, NINCDS
OTHER:	S. Kassis, Ph.D., Visiting Fellow	DMN, NINCDS
	R. V. Rebois, Staff Fellow	

COOPERATING UNITS (if any)
Laboratory of Molecular Biology, NINCDS

LAB/BRANCH
Developmental & Metabolic Neurology Branch

SECTION
Membrane Biochemistry

INSTITUTE AND LOCATION
NINCDS, IRP, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2.1	1.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) 1.Hela cells contain β-adrenergic receptors (βAR) but respond poorly to β-agonists. Cells treated with butyrate (Bu) become highly responsive and acquire more βAR. By using membrane fusion techniques, βAR from control and Bu-treated cells were shown to be equally effective in stimulating adenylate cyclase (AC) in membranes that lack βAR. Bu also induced an increase in GTP-binding components (N) as measured by cholera toxin-catalyzed ADP-ribosylation and reconstitution into cyc⁻ membranes that lack N. Both N from control and Bu-treated HeLa were able to couple AR and AC present in cyc⁻ membranes. Thus, Bu induces not only AC components in HeLa but also increased coupling of the components. 2. Incubation of membranes from human fibroblasts with either β-agonists or PGE_1 results in desensitization of AC. The process is time and temperature dependent and requires GTP. As was observed in intact cells, PGE_1 causes a heterologous desensitization whereas β-agonists cause a homologous one. 3. When exposed to hCG, murine Leydig tumor cells lose their responsiveness to hCG (desensitization), their hCG receptors (downregulation) and degrade bound hCG in that temporal sequence. Preliminary results indicate that initially the receptors become uncoupled from AC, then internalized and degraded along with bound hCG.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02433-03 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Models of Lysosomal Storage Disease.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John A. Barranger, M.D., Ph.D.	Chief, Clinical Investigations and Therapeutics Section	DMN	NINCDS
Other:	George Constantopoulos, Ph.D.	Research Biochemist	DMN	NINCDS
	Igal Gery, Ph.D.	Visiting Scientist	LVR	NEI
	F. Scott Furbish, Ph.D.	Staff Fellow	DMN	NINCDS
	Peggy Rands	Guest Worker	DMN	NINCDS
	Susan H. Sorrell	Chemist	DMN	NINCDS
	Gary J. Murray, Ph.D.	Visiting Associate	DMN	NINCDS
	Edward I. Ginns, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Norman Barton, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Roscoe O. Brady, M.D.	Chief	DMN	NINCDS

COOPERATING UNITS (if any)

Laboratory of Vision Research, NEI

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Human storage disease cells in culture and a mutant GM_1 gangliosidosis cat have been used for these studies. Study of physiologic and biochemical parameters of these models is aimed at defining the milieu in which enzyme replacement studies are conducted. Macrophages derived from circulating monocytes will survive in culture for approximately two weeks. Under special conditions, dividing cultures have been established without the use of transforming virus. These cells have survived more than six months. Alterations of lysosomal enzymatic activities have been recorded in both short and long term cultures. Estimation of lectin occurrence and function in these cells has been evaluated. The ability of cells to incorporate added lipids has been measured. Catabolism of added lipid has been compared in control and disease cells. Studies in the cat mutant have revealed that human placental β-galactosidase can be delivered to brain following blood-brain barrier opening. The placental enzyme loses about half its activity in human plasma and thus may not be ideal for enzyme replacement trials. Preparation of a more stable enzyme from feline or bovine tissues has begun. Further characterization of the cat mdoel as a model for enzyme replacement in neurological disorders is progressing.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02434-03 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Studies of Lysosomal Function: Receptor-Mediated Pinocytosis of Lysosomal Enzymes.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John A. Barranger, M.D., Ph.D.	Chief, Clinical Investigations and Therapeutics Section	DMN	NINCDS
Other:	F. Scott Furbish, Ph.D.	Staff Fellow	DMN	NINCDS
	Edward I. Ginns, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Norman Barton, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Susan H. Sorrell	Chemist	DMN	NINCDS
	Gary J. Murray, Ph.D.	Visiting Associate	DMN	NINCDS
	Peggy Rands	Guest Worker	DMN	NINCDS
	Roscoe O. Brady, M.D.	Chief	DMN	NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) The uptake of active glycoprotein lysosomal enzymes occurs, in part, through the mechanism of adsorptive pinocytosis. Receptors for various parts of the enzyme molecule as ligands are present on the plasma and organelle membranes. It is the purpose of this project to study these receptors and tuilize them for targeting enzymes to cells. These binding capacities may also play a role in localizing glycoproteins within the cell and thus may have a bearing on the survival of enzymes that have been incorporated into the cell. Studies are directed toward increasing the survival of exogenous enzymes within certain subcellular organelles. The goal is to increase the interaction of exogenous enzyme with stored material in the cell and increase the efficiency of enzyme replacement. Studied will be carried out in rats and later in human macrophages. Studies of the distribution of glucocerebrosidase confirm that infused enzyme can reach the lysosome and does not require the ligand mannose-6-phosphate (M-6-P). Moreover, hepatocytes lack a endocytic lectin with M-6-P specificity.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02435-03 DMN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Studies On The Mechanism Of Pathogenesis Of The Mucopolysaccharidoses.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	George Constantopoulos, Ph.D.	Research Biochemist	DMN	NINCDS
Other:	Roscoe O. Brady, M.D.	Chief	DMN	NINCDS
	John A. Barranger, M.D., Ph.D.	Chief, Clinical Investigations and Therapeutics Section	DMN	NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) The mucopolysaccharidoses (MPS) are a group of hereditary diseases characterized by defective metabolism of glycosaminoglycans (GAG). The disorders are usually associated with severe dysfunction of the nervous system as well as of liver, spleen, heart, bone, and other tissues. Objective of this project is the study of mechanism of pathogenesis of these diseases with emphasis on brain involvement and mental retardation. We are using a comparative approach. For this purpose we study the changes in GAG, sphingolipids, and pertinent lysosomal enzymes in tissues of patients with various types of MPS and we make correlation in terms of clinical and ultrastructural findings. Our laboratory contributed significantly in understanding the chemical pathology and in particular the neurochemistry of MPS IH, MPS IS, MPS II, MPS III A and MPS III B. To complement the studies with human subjects, a drug (suramin) induced animal model of MPS has been developed and a canine model, (natural), of MPS I is being studied. Both animal models may prove useful for understanding the pathogenesis of MPS and in the development and assessment of therapeutic trials by enzyme replacement.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02453-02 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Gaucher's Disease: Biochemical and Clinical Studies.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John A. Barranger, M.D., Ph.D.	Chief, Clinical Investigations and Therapeutics Section	DMN	NINCDS
	Roscoe O. Brady, M.D.	Chief	DMN	NINCDS
Other:	F. Scott Furbish, Ph.D.	Staff Fellow	DMN	NINCDS
	Edward I. Ginns, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Daniel Stowens, M.D.	Clinical Associate	DMN	NINCDS
	Norman Barton, M.D., Ph.D.	Clinical Associate	DMN	NINCDS
	Shutish C. Patel, M.D.	Medical Staff Fellow	DMN	NINCDS
	Susan H. Sorrel	Chemist	DMN	NINCDS
	Gary J. Murray, Ph.D.	Visiting Associate	DMN	NINCDS
	Peggy Rands	Guest Worker	DMN	NINCDS
	Carol Moore	Biologist	DMN	NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8	6	2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Glucocerebrosidase from human placenta has been purified to homogeneity and characterized kinetically. The carbohydrate content of the purified protein is 6%; composition and structure of the sugar moieties have been estimated. The molecular weight of the enzyme is 67,000 daltons. Several different isoelectric forms of the enzyme from white cells have been identified. Further work led to the identification of multiple allelic mutations in Gaucher's disease which distinguish the clinical sub-types. These isozymes differ in molecular weight and preliminary evidence suggests they are processed differently during synthesis. Polyclonal and monoclonal antibodies have been raised to enzyme and work is in progress to isolate the gene. Clinical studies in the disease have (1) identified an immune defect, (2) further characterized the hepatic complications and (3) described a rational approach to the neurologic symptoms by an analysis of the neuropathology and responses to a number of neurotransmitter agonists and antagonists. Serum lipoprotein abnormalities and the role of the macrophage in manifestations of the disease are being studied. Pathogenesis of the bone lesions are being defined and therapeutic strategies have been indicated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02529-01 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Development of Enzymes That Inactivate Neurotoxic Agents

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. O. Brady, Chief	DMN	NINCDS
OTHER:	J. M. Poston	LB	NHLBI
	A. E. Gal	DMN	NINCDS

COOPERATING UNITS (if any)
Laboratory of Biochemistry, NHLBI

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Enzymology and Genetics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An enzyme that degrades barbital has been identified and partially purified from extracts derived from a soil microorganism. The requirements for maximal catalytic activity are being determined. The ability of this enzyme to reverse lethal quantities of barbital will be investigated in toxicological experiments with appropriate animals. If this approach proves successful, enzymes that inactivate other neurotoxins will be developed in this fashion.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER ZO1 NS 02530-01 DMN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Non-sensitizing Thrombolytic Enzyme Preparations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Newmark	DMN NINCDS
OTHER:	R. O. Brady, Chief	DMN NINCDS
	A. Abuchowski	Rutgers University
	G. Murano	Bu. Biologics, FDA

COOPERATING UNITS (if any)

Department of Biochemistry, Rutgers University
New Brunswick, NJ

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Enzymology and Genetics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Adducts of streptokinase and streptokinase-plasminogen complex with polyethylene glycol and the pluronic polyol F38 were prepared with the aim of developing a non-sensitizing form of streptokinase. The adducts were much less antigenic than the native protein or protein complex. Full amidolytic activity was retained when catalysis was measured with a chromogenic substrate. However, dissolution of fibrin clots by the adducts was greatly reduced from that obtained with native streptokinase.

TAB 19 -- EXPERIMENTAL THERAPEUTICS BRANCH -- ETB/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Experimental Therapeutics Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Experimental Therapeutics Branch, IRP
National Institute of Neurological and Communicative Disorders and Stroke
Thomas N. Chase, M.D., Acting Chief

The past year has witnessed several important changes in Branch organization and activities. Dr. Donald B. Calne, former Branch Chief left NIH for an academic post in Vancouver, Canada. His Therapeutics Section, which has continued active under the leadership of Dr. Peter LeWitt, will be discontinued at the end of this fiscal year. A search for a new ETB Chief has now been initiated. The Branch moved from its Building 36, 5A corridor and Building 10, 6D corridor facilities to contiguous laboratory and office space on the 5th floor of the ACRF. Despite these changes, the basic thrust of the Branch's scientific activities, directed towards the improved treatment of neurologic disease, has remained essentially unchanged.

BIOCHEMICAL NEUROPHARMACOLOGY SECTION

1. Direct Identification of the D-2 Dopamine Receptor in the Intermediate Lobe of the Rat Pituitary Gland

The hypothesis that two categories of dopamine receptors exist continues to gain support. It was especially gratifying that the paper putting forward the two dopamine receptor hypothesis was the second most highly cited Life Science paper in the period 1979 to 1981. In FY '81 the efforts of the section were directed towards providing experimental evidence to back up this hypothesis.

In FY '81, experiments were performed to directly identify the D-2 dopamine receptor in the intermediate lobe (IL) of the rat pituitary gland. The rationale behind these experiments was to use radiolabeled spiroperidol to identify specific binding sites in the IL and to compare the properties of the specific binding site to the properties of the dopamine receptor inhibiting adenylate cyclase activity (which had been characterized in FY '80). The experimental conditions used in the binding assays replicated (as closely as possible) the experimental conditions used to determine adenylate cyclase activity in order to facilitate the comparison of the data obtained in the two different assays.

The IL of the rat pituitary gland contains 16 fmole of high affinity specific spiroperidol binding sites. The density of these binding sites in the IL (8.3 pmole/g tissue) is equivalent to the density of spiroperidol binding sites in the neostriatum. The properties of the IL spiroperidol binding sites have been characterized in experiments testing the ability of various drugs to compete with the radiolabeled ligand for occupancy of the specific binding site. With the exception of (-)-sulpiride, the rank order of potency of dopaminergic compounds in the spiroperidol binding assay and the adenylate cyclase assay were similar. Furthermore, for each drug tested, the apparent affinity constant derived from the two assays agrees within an order of magnitude. Therefore we have adopted the "working hypothesis" that some or all of the specific spiroperidol binding sites in the IL are the dopamine receptors inhibiting

adenylate cyclase activity in the homogenates of IL tissue. In contrast to the good agreement obtained in the two biochemical assays, the intact IL cells respond to agonists at 100-fold lower concentrations than are required to elicit either biochemical response in the cell-free assay systems. A similar discrepancy is encountered for the beta-adrenoceptor in the IL. An understanding of the basis for these discrepancies may add to our understanding of the biochemical basis for dopamine receptor activity.

The binding experiments in the intermediate lobe are of some theoretical interest. Although binding experiments claiming to identify dopamine receptors are extremely popular, the value of this approach is limited because there are few in vitro measurements with which the results of the binding experiments can be compared. However, in the case of the experiments performed with the intermediate lobe, the data can be compared with the results obtained from adenylate cyclase assays which were performed under identical conditions. It might be anticipated that the data obtained in the intermediate lobe would provide the standard against which other dopamine receptor binding studies would be compared.

2. Coordinated Action of Calcium and cAMP on the Release of Alpha-MSH from the IL

Calcium and cyclic AMP participate in the specific cellular events leading to secretion from a variety of cells. Previous investigators had shown that calcium was essential for the stimulated release of alpha-MSH from the intermediate lobe. During FY '81, calcium was shown to participate in the release of alpha-MSH elicited by a variety of drugs affecting cyclic AMP metabolism. Thus, calcium was essential for the L-isoproternol-, the 3-isobutyl 1-methylxanthine-, or the cholera toxin-induced release of alpha-MSH. In the case of each drug tested, a fixed concentration of calcium elicited more release from cells with enhanced synthesis or content of cAMP.

3. YM-09151-2, a Selective D-2 Antagonist

YM-09151-2, (cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methyl-aminobenzamide), a substituted benzamide, was shown to be a potent antagonist of the dopamine receptor in the intermediate lobe of the rat pituitary gland. Assuming that YM-09151-2 and dopamine compete for occupancy of the D-2 receptor, the affinity of the interaction between the antagonist and the receptor was calculated as 10.5 nM. YM-09151-2 was approximately equipotent with fluphenazine as a dopamine antagonist, and was significantly more potent than the other substituted benzamides tested. YM-09151-2 was found to be an extremely weak antagonist of the D-1 receptor in the fish retina. Therefore because YM-09151-2 can discriminate between these two categories of dopamine receptor, it may prove to be a useful tool for investigating the pharmacology of the receptors mediating the physiological effects of dopamine.

4. A D-2 Dopamine Receptor in the Neostriatum

Previously, we had proposed that in the neostriatum both D-1 and D-2 dopamine receptors regulate the efflux (and by inference the formation) of cyclic AMP. Stimulation of the D-1 receptor increases the formation of cyclic AMP. Stimulation of the D-2 dopamine receptor reduces the cAMP formation stimulated by D-1 agonists. Based on experiments performed in FY '81, we hypothesize that the inhibitory effect of D-2 agonists upon cyclic AMP formation results from a direct interaction between the D-1 and the D-2 receptor. This conclusion is based on the observation that the inhibitory effect of D-2 agonists persists in the absence of calcium ions in the superfusion medium.

Previously, selective D-2 dopamine receptor agonists had been shown to cause an accumulation of acetylcholine in the neostriatum of the rat brain. In the present experiments, selective D-2 receptor agonists were shown to inhibit the potassium-evoked release of acetylcholine. In contrast, the selective D-1 agonist, SKF 38393, did not inhibit acetylcholine release. The inhibitory effect of the D-2 agonists could be reversed with (-)-sulpiride. These observations suggest that the in vivo accumulation of acetylcholine may arise as a consequence of diminished release of acetylcholine. Such an action of selective D-2 agonists may be of theoretical interest for the treatment of Parkinson's disease. A balance between the dopaminergic and the cholinergic system is thought to participate in the regulation of extrapyramidal function by the neostriatum. The deficiency of neostriatal dopamine occurring in Parkinsonism disrupts this balance between dopamine and acetylcholine. It is conceivable that the D-2 dopaminergic agonists used in the treatment of Parkinsonism (e.g., bromocriptine, lergotrile or lisuride) may achieve some of their therapeutic effect by interacting with a D-2 dopamine receptor on cholinergic interneurons, inhibiting the release of acetylcholine and restoring the balance between dopaminergic and cholinergic function in the neostriatum. However, the selective D-2 agonists may have additional effects entirely unrelated to cholinergic activity in the neostriatum (the inhibition of the efflux of cyclic AMP stimulated by D-1 agonists is an example of such an effect of D-2 agonists).

PHYSIOLOGICAL NEUROPHARMACOLOGY SECTION

1. Physiological effects of dopamine and dopamine agonists in the basal ganglia.

To gain insight into how dopamine and the dopamine agonists affect information processing in the basal ganglia, we have been examining the effects of these agents at sites where information funnels out of the basal ganglia, the pars reticulata of the substantia nigra and the globus pallidus. The actions of dopamine agonists at these sites have been compared with their effects on the activity of dopamine neurons themselves.

a. Substantia Nigra Pars Reticulata Studies

We have continued our investigations of the direct and indirect effects of dopamine and dopamine agonists on the activity of tonically firing neurons in the substantia nigra pars reticulata, concentrating on confirming and extending our earlier observation that iontophoretically-applied dopamine can consistently and markedly diminish the inhibitory effects of iontophoresed gamma-aminobutyric acid (GABA) on the neurons in this region. The consistent modulatory interaction of dopamine and GABA appears, to date, to be specific for these two transmitters. Iontophoretically-applied dopamine has more variable effects upon responses of reticulata cells to glycine. Similarly, no consistent modulatory interactions have been detected between dopamine and either of two transmitters known to stimulate reticulata cell firing, acetylcholine and glutamic acid. These results demonstrate that the potential exists for dopamine, released from dendrites within the pars reticulata, to serve an important local function, downstream from the striatum, adjusting or "fine-tuning" the relay of striatal commands to premotor nuclei outside the basal ganglia.

Studies were undertaken to determine whether similar modulatory interactions between dopamine and GABA could occur as a consequence of endogenous local release of dopamine from dendrites of neighboring pars compacta dopamine neurons. d-Amphetamine, a drug reported to induce release of dopamine from dendrites within the substantia nigra, could also attenuate responses of reticulata neurons to GABA. This effect was found to be dependent upon the existence of an intact dopamine system in the substantia nigra. Moreover, studies in rats with lesions of the dopamine neurons, indicate that the dopamine receptors involved in the modulatory interaction may ultimatley become supersensitive in a dopamine deficient substantia nigra.

The ability of amphetamine to attenuate reticulata cells' responses to GABA, observed in rats with intact nigral dopamine systems, provides evidence of a physiological role of dopamine, presumably released from dendrites, as a modulator of GABA effects on substantia pars reticulata neurons projecting to pre-motor nuclei outside the basal ganglia. However, the observation that amphetamine could induce changes in the baseline firing rates of reticulata cells, even in rats with apparently effective unilateral lesions of the nigrostriatal dopamine pathway, suggested that this drug can also alter the activity of these neurons by other mechanisms.

b. Globus Pallidus Studies

In the globus pallidus, as in the substantia nigra, we have confirmed and extended our previous finding that dopamine modulates GABA-induced inhibition of pallidal activity. Since the dopamine neurons of the substantia nigra pars compacta are known to send a sparse but widespread projection to the globus pallidus, it seemed possible that endogenous dopamine might be able to exert a similar modulatory effect on the actions of GABA in this brain region. It was found that after amphetamine administration, 45% of the cells recorded showed attenuated responses to iontophoresed GABA. These results suggest that under normal conditions,

pallidal dopamine may be able to exert a modulatory effect on the actions of GABA released from striatopallidal fibers. This ability of endogenous dopamine to modulate GABA's effects in the globus pallidus may also contribute to the pharmacological effects of systemically-administered dopamine agonists in the basal ganglia.

In the past year, we have continued our investigations of the effects of systemically administered dopamine agonists on the activity of tonically firing pallidal neurons, since pallidal cells are in a good position to reflect the net effects of these drugs on dopamine receptors at several sites in the basal ganglia. Results from studies with norepinephrine and serotonin agonists suggest that dopamine receptor stimulation is more effective than serotonin or norepinephrine receptor stimulation at inducing increases in pallidal activity. The effects of dopamine agonists with putatively selective actions at specific subcategories of dopamine receptors were also examined. There is currently considerable interest in the possibility that there may be subtypes of the D-2 receptor (such as the presynaptic dopamine receptor) with specific functions which could be differentially manipulated pharmacologically. If dopamine agonists selective for some of these dopamine receptor subtypes can be found, it is hoped they might be useful in the treatment of disorders such as tardive dyskinesia or schizophrenia. Pallidal effects of SK&F 38393, a drug which preferentially stimulates D-1, as opposed to D-2, dopamine receptors in the striatum, and 3-PPP, a drug thought to preferentially affect presynaptic dopamine receptors, have been investigated. The results suggest that drugs thought to be effective at selectively stimulating D-1 or presynaptic dopamine receptors do not significantly alter pallidal firing rates. The increase in pallidal activity which have been observed with apomorphine, lisuride and pergolide administration appear to be related to their postsynaptic D-2 dopamine receptor stimulating properties. Comparisons of the effects of dopamine agonists on the activity of dopamine cells and pallidal neurons may provide useful information about the in vivo selectivity of new dopamine agonists and antagonists and help establish the physiological relevance of the various binding and biochemical tests currently used to screen for agents with selective dopamine agonist properties.

We have also continued in the past year to explore a second aspect of the effects of apomorphine on the activity of tonically firing pallidal neurons. As reported previously, the administration of small non-excitatory doses of this drug has an apparent priming effect on the system; subsequent administration of larger doses which would normally cause a significant excitation of the cells' activity now causes only a small change in firing rate. Since it seemed possible that this priming effect of apomorphine might provide insight into the mechanism behind the paradoxically useful effects of dopamine agonists in treatment of tardive dyskinesia and schizophrenia, we have explored it further. Studies have shown that the phenomena is not unique for apomorphine; similar results have been observed with a second dopamine agonist, lisuride. In addition, a priming dose of apomorphine has been shown to alter the response of the pallidal neurons to amphetamine and haloperidol. Binding studies have

been undertaken to determine whether small doses of a dopamine agonist can alter the ability of the striatum and globus pallidus to bind spiroperidol, in vitro, but the results have been inconclusive to date.

2. Physiological effects of GABA and GABA agonists in the basal ganglia.

In our previous investigations of the role of the striatonigral GABAergic pathway in the substantia nigra, we found that benzodiazepines, drugs thought to act by potentiating the effects of GABA, have inhibitory effects on the firing rates of neurons in the substantia nigra pars reticulata. Recent findings from studies of the interactions between GABA agonists and antagonists, and the benzodiazepines are consistent with previous reports which suggest that the benzodiazepines may act through a GABAergic mechanism. While it has been proposed that the benzodiazepines may also act by blocking the reuptake of adenosine, thereby potentiating the depressant action of this endogenous inhibitory substance, results from our iontophoretic studies suggest that a potentiation of adenosine's actions cannot account for the inhibitory effects of the benzodiazepine on pars reticulata neurons. Additional studies with RO 15-1788, an imidazodiazepine thought to function as a specific benzodiazepine antagonist suggest that cells of the substantia nigra pars reticulata do not receive a substantial tonic inhibition mediated by an endogenous benzodiazepine-like substance. They also indicate that the methylxanthines increase reticulata cell firing, at least in part, through mechanisms unrelated to the blockade of benzodiazepine receptors.

PHARMACOLOGY SECTION

1. Positron Emission Tomography Studies

Regional neuronal activity has now been studied in 12 patients with clinically diagnosed Alzheimer's disease by means of positron emission tomography (PET) following intravenous 18-F-2-fluoro-2-deoxyglucose administration. These investigations seek to correlate various aspects of cognitive function with regional cortical metabolic activity. Results to date indicate that performance on standardized tests of general cognitive function tend to correlate with overall cortical metabolic rates for glucose. Moreover, patients with aphasia out of proportion to their other cognitive deficits had substantial reductions in glucose utilization in the left temporal and parietal regions; those with disproportionately severe constructional apraxia evidenced a prominent hypometabolic focus involving the right parietal lobe. Combined results from all patients studied thus far suggest that the cortical distribution of regions in which there is a close positive correlation between language performance and cerebral metabolism, while varying with the specific function tested, tend to cluster in the left frontal, temporal, and parietal areas. On the other hand, the cortical localization of regions having a close association between visuo-constructive test performance and glucose metabolism tended to aggregate in the posterior right hemisphere. Since these localizations generally agree with those provided by other means, attempts to map a broad range of cortical functions have now begun. Future applications of the fluorodeoxyglucose - positron emission tomographic technique will be directed towards the validation--by means of various pharmacologic and physiologic manipulations of cerebral function--

of the localizing hypothesis generated by the present investigations, as well as the search for regional abnormalities in neuropsychiatric disorders, such as dystonia and Tourette's syndrome, where no pathologic changes have been found to account for clinical symptoms.

2. Cerebrospinal Fluid

During the past year it has been found that the administration of the experimental GABA agonist, THIP, is associated with a significant elevation in CSF homovanillic acid, the major metabolite of dopamine. This observation suggests that THIP may stimulate dopaminergic function and could explain the lack of antidyskinetic efficacy of this agent.

3. Dopamine Agonists

The ability of dopamine receptor agonists to ameliorate hyperkinetic extrapyramidal disorders continues to be evaluated. These investigations are based on the hypothesis that dopamine agonists which preferentially stimulate dopamine autoreceptors might inhibit dopaminergic transmission and thus diminish neurologic and psychiatric symptoms reflecting hyperfunction of this system. Since data supporting this contention in part derive from previous experience with apomorphine, current studies have focused on n-propylnorapomorphine (NPA), a relatively non-toxic apomorphine derivative, suitable for oral administration. Results from an acute, rising dose, double-blind, placebo-controlled study revealed antipsychotic and antianxiety activity in a group of drug-free schizophrenic patients. In each patient the antipsychotic response to NPA appeared to correlate with their response to neuroleptic drugs, supporting the view that NPA may act at the dopamine autoreceptor to mimic the clinical effects of neuroleptics. An extension of these studies to patients with tardive dyskinesia is now planned. In addition, a new and apparently extremely selective dopamine autoreceptor agonist, EMD 23 448, will now be tested in similar manner for evidence of antipsychotic and antidyskinetic activity.

4. GABAmimetic Drugs

Based on preclinical biochemical and pharmacologic observations suggesting that augmentation of GABA-mediated synaptic function may benefit patients with tardive dyskinesia and related naturally occurring or drug-induced hyperkinetic extrapyramidal disorders, clinical studies of two experimental GABAmimetic compounds have been conducted during the past year. Gamma-vinyl GABA blocks GABA degradation in the brain, by inhibiting GABA-transaminase. Five patients with tardive dyskinesia, who were free from other centrally active medication, have now been evaluated during the oral administration of this compound. All evidenced some diminution in their dyskinesia. Since no significant side effects occurred, studies with this compound will continue. In addition, the therapeutic efficacy of orally administered THIP, a selective GABA receptor agonist, has been evaluated in four patients with classical Huntington's disease and one with the rigid-akinetic form of this disorder. No consistent improvement in motor or cognitive function was observed. At maximum dose levels, however, THIP mimicked another putative GABA agonist, muscimol, in producing unsteadiness of gait, diminished

attention to sensory stimuli, and somnolence, thus supporting the view that central GABA systems participate in the regulation of certain motor and behavioral functions in man.

5. Cholecystokinin

Laboratory studies with cholecystokinin octapeptide (CCK-8) have sought to extend previous findings and identify the central mechanism of CCK-8 interaction with the dopamine system. CCK-8 occurs in some dopamine-containing neurons and thus might affect dopamine-mediated synaptic transmission. Our previous observation that systemically administered CCK-8 possesses some neuroleptic-like activity has now been confirmed and extended. The neuroleptic-like effects occur at relatively low dose levels and are not mimicked by tetragastrin, a 4 amino acid peptide possessing most of the gut actions of CCK-8. This latter finding supports the view that the behavioral effects of CCK-8 reflect a centrally mediated response to the peripherally administered neuropeptide. Recent studies also indicate that tolerance may occur in avoidance paradigms to the repeated administration of CCK-8; the mechanism of this effect is now being investigated. In related studies the structure-activity relationships of sulfated, N-terminal analogues of CCK-8 are being explored. One such CCK-8 fragment appears to antagonize the effects of CCK-8 when tested in the pancreatic acinar cell bioassay, suggesting that products of CCK-8 degradation may inhibit the primary action of the parent peptide.

6. Substance P

Laboratory investigations of the behavioral effects of systemically administered substance P and several of its biologically active fragments have remained active in collaboration with the Department of Psychology, University of Colorado. Studies during the past year have revealed that the subcutaneous post-trial administration of the neuropeptide reverses the amnestic effects of electroconvulsive shock or cycloheximide in both inbred and genetically heterogeneous mice. Peripheral injection of substance P was also found to facilitate the retention of a single-trial passive avoidance habit in animals of both genotypes, provided a weak foot-shock was used during training. Further studies are now planned to elucidate the mechanisms by which exogenously administered substance P may influence memory processing in the mammalian central nervous system.

7. Neuroendocrine

Additional evidence of hypothalamic dysfunction in Huntington's disease (HD) has been found during the past year. Our results now indicate that circulating daily growth hormone levels are significantly elevated in HD women as compared with matched controls, and further that a higher peak response occurs with either dopamine agonist (apomorphine) or GABA agonist (muscimol) stimulation in male or female HD patients than in control subjects. Since no consistent abnormalities in basal or stimulated prolactin levels were found, it appears unlikely that dopamine system hyperactivity could account for the growth hormone changes. The search for alternative explanations led to measurements of somatostatin (SRIF), the hypothalamic hormone which inhibits growth hormone release, in

the suprachiasmatic hypothalamus. While SRIF levels tended to be lower in HD subjects, no statistically significant difference could be documented in the small number of cases assayed to date.

THERAPEUTICS SECTION

1. Antiparkinson Efficacy of Pergolide

A study of 27 patients has been completed in which bromocriptine and pergolide therapy was compared in a double-blind, crossover fashion. Each drug was tested to optimal dose, which varies over a tenfold range. Efficacy against parkinsonian symptoms, and the spectrum of adverse reactions, were similar. Thirteen patients previously underwent comparison of lisuride and bromocriptine in an identical study format, permitting comparison among the three drugs. One patient developed hepatotoxicity and pleural reaction to the drugs, while other adverse symptoms included "benign" hallucinations and other side effects previously observed with lisuride and bromocriptine. Long-term follow-up of pergolide treatment has established its continuing efficacy and safety for over one year.

2. Therapy of Parkinsonism with Tetrahydrobiopterin (THB)

Earlier studies showing decreased levels of THB in the cerebrospinal fluid of parkinsonian patients suggested that this cofactor might have therapeutic potential for this condition. THB is a substrate for tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis. In collaboration with NHLBI scientists, the entry into the central nervous system and biochemical effects of THB administration have been studied in animals. With evidence of entry and effect on the dopamine system, THB was administered parenterally on three successive days to two parkinsonian volunteers. Neither clinical improvement nor toxicity resulted. Biochemical studies of cerebrospinal fluid are currently under analysis.

3. Therapeutics of Movement Disorders Related to Parkinsonism

Progressive supranuclear palsy (PSP) and dystonia are disorders involving the extrapyramidal system and sharing some features with parkinsonism. Using dopaminergic ergot derivatives previously proven effective in parkinsonism (bromocriptine and lisuride), therapeutic trials have been undertaken. In 12 patients with dystonia and poor response to conventional therapy, bromocriptine has been shown, in a double-blind study,to offer improvement from clinical symptoms and functional disability. Initial results indicate that this medication is well tolerated and compatible with other agents sometimes effective in dystonia, such as anticholinergic drugs and clonazepam. In some patients, the clinical impression is of synergy between these agents. No significant toxicity has been encountered.

PSP therapy with lisuride has been initiated in five patients. Improvement of rigidity and bradykinesia has been encountered, as well as improvement of voice and swallowing abilities. Most of the patients have been quite sensitive to the medication, and a few have exhibited toxicity such as hallucinations. Nevertheless, the use of this therapy, in

combination with anticholinergic medication, may offer benefit to patients, who generally are unresponsive to levodopa.

4. Studies of Therapeutics and Mechanisms of Essential Tremor

Current work has investigated the mechanisms and treatment of essential tremor. Studies have involved electromyographic recording techniques, and testing of the role of the adrenergic system in tremor by infusion of isoproterenol. Four patients with stable essential tremor have undergone such testing, indicating that peripheral beta-receptor sensitivity is normal in essential tremor. In one patient with severe essential tremor, and no response to propranolol, a normal peripheral action of propranolol was demonstrated. Six essential tremor patients have undergone studies measuring amine transmitters and metabolites from plasma, urine, and cerebrospinal fluid. Three patients have been treated with clonidine, a drug with pre-synaptic adrenergic effects in the brain; preliminary results are promising.

Electromyographic activity of agonist and antagonist muscles in the forearm has been studied in 4 essential tremor patients. Contrary to previous reports in the literature, simultaneous activity in antagonist muscle groups was not found. Rather, there was alternate activity of action potential bursts in phase with the tremor frequency. An additional study has shown that propranolol suppresses fatigue tremor in normal subjects.

5. Binding Receptors in Human Brain

Ligand binding of striatal neurotransmitter receptors (encephalin, dopamine, beta-neurotensin, and diazepam) was studied in autopsy brain specimens from 5 parkinsonian patients, 4 controls, and 2 schizophrenic patients. Preliminary studies show decreased binding of dopamine, encephalin, and neurotensin ligands in parkinsonian brains.

6. Studies with Thyrotropin-releasing Hormone in Ataxic Disorders

Following promising results from research in Japan, 13 patients have been treated with parenteral thyrotropin releasing hormone (TRH). In responders, further studies were planned with cholinergic medications and with analogues of TRH. One responder was identified, but subsequent testing in a double-blind protocol failed to sustain this impression of improvement.

7. Decarboxylation of Levodopa in Dyskinetic Parkinsonian Subjects

Using a technique of analyzing radio-labeled carbon dioxide excreted after administration of labelled levodopa, parkinsonian patients have been studied in regard to adverse reactions with levodopa, such as "on-off" phenomenon and dyskinesia. Findings confirm earlier impressions that fluctuations response to levodopa are independent of the rate of decarboxylation. These studies, conducted in collaboration with NIMH scientists, have also suggested that blockade of peripheral decarboxylation during levodopa therapy is not reduced linearly with increasing doses of carbidopa.

CLINICAL EPILEPSY SECTION

1. Diagnostic and Therapeutic Reevaluation of Patients with Intractable Epilepsy.

The Clinical Epilepsy Section has been developing and testing new techniques to achieve improved seizure control, reduce drug-induced side effects, and achieve better rehabilitation in patients with severe epilepsy. These include simultaneous video and telemetered EEG recording of seizures, daily determination of antiepileptic drug serum concentration, and most recently, the concomitant use of positron emission tomography.

The use of positron emission computer tomography (PECT) may greatly alter our understanding of localized brain lesions in patients with partial seizures. Current studies, limited to metabolic evaluations using F^{18}2-deoxyglucose, demonstrate focal hypometabolic cerebral areas corresponding to the interictal seizure EEG focus. During a seizure, this region is converted from a hypometabolic to hypermetabolic focus. Focal PECT lesions may be identified in some patients even if the EEG abnormality itself is not well localized. In other cases, an ictal PECT scan may clarify the results of an equivocal interictal scan. These studies allow more definitive overall identification of the localization of the epileptic lesion and permit a more precise surgical approach to patients with partial seizures, patients who are often refractory to medical therapy. The PECT scan is noninvasive and lesions are often documented in patients whose neurological examinations and CT scan are normal.

Intensive monitoring with simultaneous video and EEG recordings continue to elucidate new areas of seizure classification and differentiation. Studies recently concluded are those of the clinical characteristics of complex partial seizures, and of psychogenic (non-epileptic) seizures; in both cases the differential diagnosis is very important to appropriate therapy. Intensive monitoring has been useful in an on-going study of secondary generalization, and its effectiveness in intractable epilepsy has been documented.

The study of evoked responses in patients with epilepsy has new investigations of patients with intractable seizures. Early studies have shown that the dominant eye may greatly influence the amplitude of the visual evoked response, an important feature to recognize in all patients. In addition, patients with complex partial seizures are currently being evaluated for abnormalities of the visual evoked response, auditory and brainstem evoked potentials, and the somatosensory evoked potentials. Evoked potentials are also being utilized in the evaluation of new drugs.

Finally, the video-taped seizures at the Clinical Epilepsy Section have formed the basis of an unparalleled library of seizures for teaching and analysis. In collecting these seizures, the Clinical Epilepsy Section is constantly making technical advances in intensive monitoring.

2. Clinical Pharmacology of Antiepileptic Drugs

Pharmacologic studies in epilepsy have concentrated on studies of drug interactions and of new antiepileptic drugs.

Nine normal volunteers have participated in a pharmacokinetic study of Progabide, a new drug being evaluated for epilepsy which is already being tested in eight European countries. The drug is a putative GABA agonist and its mechanism of action may be through its effect on this inhibitory transmitter. Preliminary results confirm linear kinetics and dose proportionality.

A new potential antiepileptic agent, flupirtine, is in the final stages of testing in Germany as an analgesic. The structure of the compound is completely different from currently marketed antiepileptic drugs. The drug is effective in animal models of epilepsy which suggest that it may be effective in partial seizures or absence seizures. The Clinical Epilepsy Section is studying both of these seizure types in different patients in an open pilot study of intensive design. Preliminary results show a promising decrease in seizure frequency in some patients. It is likely that the current upper limit of dose is inadequate to obtain maximal seizure control; planning is underway to arrange for higher doses.

A number of studies have been performed in drug-drug interactions of antiepileptic drugs. A study of the interaction between phenytoin and primidone demonstrated that metabolite levels of primidone are altered by the phenytoin, with the major effect being a direct inhibition of the metabolite phenobarbital by phenytoin. In a different study, the interaction between valproic acid and phenobarbital was studied in which valproic acid also inhibited phenobarbital metabolism. In order to evaluate the mechanism of this effect, the influence of valproic acid on acetaminophen was studied, and this demonstrated that the effect on phenobarbital is likely to be inhibition of hydroxylation rather than glucoronidation. A study evaluating the effect of carbamazepine on phenytoin has been carried out using heavy-labeled phenytoin in which the pharmacokinetic parameters of phenytoin have been determined before and after the addition of carbamazepine. This study shows that carbamazepine interacts and increases the plasma levels of phenytoin when these drugs are given in combination. Recently completed studies include those on the effect of food on drug absorption and the effect of total removal of sedative-hypnotic antiepileptic drugs from patients with severe epilepsy.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02263-06 ET

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biochemical and Pharmacological Studies of Dopamine Receptors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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COOPERATING UNITS (if any)

None

LAB/BRANCH

Experimental Therapeutics Branch

SECTION

Biochemical Neuropharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.8	8.8	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINDRS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates the biochemistry of dopamine receptors. Using the insight gained about the biochemical basis of dopamine receptor function, drugs selectively interacting with the various subcategories of dopamine receptor are identified and characterized. The availability of drugs selectively stimulating or blocking the various subcategories of dopamine receptor will be useful in the treatment of Parkinson's disease, endocrine disorders, psychiatric disorders, hypertension and as antiemetics in cancer chemotherapy. Among the topics studied during the current fiscal year are: binding of spiroperidol to the D-2 dopamine receptor in the intermediate lobe of the rat pituitary gland; characterizing the D-2 dopamine receptor regulating acetylcholine release and cyclic AMP synthesis in the striatum; identifying YM-09151-2 as a selective D-2 antagonist; identifying the coordinated role of calcium ions and cyclic AMP in the intermediate lobe of the rat pituitary gland and investigating the hypothesis that drugs can discriminate between the pre- and postsynaptic dopamine receptors.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02139-08 ET

PERIOD COVERED
October 1, 1981 through September 20, 1982

TITLE OF PROJECT (80 characters or less)

Pharmacology and Physiology of Central Neurotransmitters

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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COOPERATING UNITS (if any)

None

LAB/BRANCH
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.2	2.7	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop an understanding of the role of specific neurotransmitters in basal ganglia function, with the goal of developing improved strategies for pharmacological treatment of neurological disorders. Topics currently under investigation include (1) the ways in which systemically administered dopamine agonists may affect neuronal activity in the pars reticulata and pars compacta of the substantia nigra and in the globus pallidus; (2) the ability of iontophoresed dopamine to modulate the actions of other neurotransmitters in these brain regions and (3) effects of GABA, GABA agonists, and drugs, such as the benzodiazepines which modulate GABA's effects on the activity of identified regions of the basal ganglia and substantia nigra.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02265-06 ET

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pharmacology, Biochemistry and Physiology of Central Neurotransmitters

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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LAB/BRANCH
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NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.25	2.75	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to develop improved drug therapies for nervous system disease. Clinical and preclinical investigations seek to elucidate how the activity of specific transmitter systems relate to neuropsychiatric function. Based on these relationships, novel pharmaceutical agents are evaluated for their ability to influence central synaptic processes and thus modify neurologic symptoms. Major topics now under study include: 1) evaluations of human transmitter system function in the brain generally (through assays of endogenous or radioactively labelled transmitters or their metabolites in spinal fluid) or locally (by means of positron emission tomography using the fluorodeoxyglucose method), and 2) preclinical and clinical tests of the ability of selected dopamine agonists, GABAmimetics, and neuropeptide analogs to influence motor and cognitive behavior.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02258-06 ET

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Therapeutic Studies in Parkinsonism and Other Movement Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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COOPERATING UNITS (if any)
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LAB/BRANCH
Experimental Therapeutics Branch

SECTION
Therapeutics Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	3.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The therapeutics of parkinsonism and related neurological disorders has been the goal of projects assessing the efficacy and safety of new drugs in clinical studies. These investigations have provided insight into biochemical and physiological disturbances underlying movement disorders. Conclusions reached over the past year include: (1) two new ergot derivatives, lisuride and pergolide, have comparable clinical profiles against parkinsonism despite their pharmacological differences. Our pharmacokinetic studies with lisuride offer explanations for variability in effects of the drug; (2) tyrosine hydroxylase cofactor, deficient in parkinsonism, produced increased dopamine synthesis in animals. However, parenteral administration to parkinsonian patients was without benefit; (3) two movement disorders with parkinsonian features but generally without response to L-DOPA, dystonia and progressive supranuclear palsy, have responded in some instances with dopaminergic ergot therapy; (4) clonidine therapy may be effective in essential tremor. Peripheral adrenergic mechanisms do not differ from normals, as shown by isoproterenol testing; (5) binding studies show other neurotransmitter substances (in addition to dopamine) to be decreased in parkinsonian brain.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02236-07 ET

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Diagnostic and Therapeutic Reevaluation of Patients with Intractable Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Porter	Acting Chief, Clinical Epilepsy Section	ET	NINCDS
OTHERS:	E.S. Gratz	Medical Staff Fellow	ET	NINCDS
	W.H. Theodore	Neurologist	EB	NINCDS
	R. Long	Video Engineer	EB	NINCDS
	H.J. Kupferberg	Pharmacologist	EB	NINCDS

COOPERATING UNITS (if any)
Epilepsy Branch, NDP, NINCDS; Office of Administrative Management, Clinical Center, NIH

LAB/BRANCH
Experimental Therapeutics Branch

SECTION
Clinical Epilepsy Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Clinical Epilepsy Section has been developing and testing new techniques to achieve improved seizure control, reduce drug-induced side effects, and achieve better rehabilitation in patients with severe epilepsy. These include simultaneous video and telemetered EEG recording of seizures, daily determinations of antiepileptic drug serum concentrations, and most recently, the concomitant use of positron emission tomography. Patients with very long histories of uncontrolled seizures are admitted for a complete evaluation, including all basic neurologic studies and daily objective toxicity battery. Intensive monitoring techniques are used to establish a seizure diagnosis, which is then utilized to design an appropriate therapeutic regimen for each patient. The study of positron emission computerized tomography (PECT) in patients with localized brain lesions has demonstrated focal hypometabolic cerebral areas corresponding to the interictal seizure EEG focus. Such studies allow more definitive overall identification of the localization of the epileptic lesion and suggest new avenues of investigation into the basic mechanisms of the epilepsies.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02318-05 ET

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Clinical Pharmacology of Antiepileptic Drugs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Porter	Acting Chief Clinical Epilepsy Section	ET	NINCDS
OTHER:	E.S. Gratz	Medical Staff Fellow	ET	NINCDS
	H.J. Kupferberg	Pharmacologist	EB	NINCDS
	W.H. Theodore	Neurologist	EB	NINCDS

COOPERATING UNITS (if any)

Epilepsy Branch, NDP, NINCDS

LAB/BRANCH
Experimental Therapeutics Branch

SECTION
Clinical Epilepsy Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Clinical Epilepsy Section continues to study the clinical pharmacology of old and new antiepileptic drugs. Special emphasis has been placed on studies of two new antiepileptic compounds, progabide and flupirtine. Progabide has been studied pharmacokinetically in normal volunteers, whereas flupirtine is being evaluated both clinically and pharmacologically in patients with either complex partial or absence seizures. Flupirtine is especially promising in models of epilepsy and preliminary clinical results are encouraging. Drug interactions continue to be a major pharmacologic interest of the Section. Most recently, the interaction between phenytoin and carbamazepine has been evaluated using mass spectrometry methodology. Other studies recently completed include the interaction of phenytoin and primidone, as well as valproate and phenobarbital. The pharmacologic evaluation of these drugs is coupled with efficacy studies, carried out by intensive monitoring techniques including videotape analysis of epileptic seizures with simultaneous telemetered EEG recording, and daily determination of antiepileptic drug levels.

TAB 20 -- INFECTIOUS DISEASES BRANCH -- IDB/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Infectious Diseases Branch
National Institute of Neurological and Communicative Diseases and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1981 through September 30, 1982
Infectious Diseases Branch, IRP
National Institute of Neurological and
Communicative Disorders and Stroke

John Louis Sever, M.D., Ph.D., Chief

I. RESPONSIBILITY OF THE BRANCH

The responsibility of the Infectious Diseases Branch is to carry out planned, coordinated research programs concerned with infections which damage the human nervous system. The Branch is divided into three sections: 1) Immunochemistry and Clinical Investigations; 2) Experimental Pathology; and 3) Neurovirology. These sections utilize the techniques of immunology, clinical investigations including human volunteers and clinical trials, experimental pathology with nonhuman primates, virology, bacteriology, mycoplasmology, neurovirology, human tissue culture and electron microscopy.

II. PROGRAM SEGMENTS

The program segments are: a) perinatal; b) acute; and c) chronic. In each segment we are concerned with: 1) etiology and diagnosis; 2) treatment; and 3) prevention.

The research areas in the program segments include:

A. Perinatal

Develop and utilize large scale methods to study the relation between viral, bacterial, mycoplasmal and protozoal infections in the perinatal period and birth defects, related abnormalities and pediatric neurological diseases. Investigate approaches to early diagnosis, treatment and prevention using combined laboratory and clinical studies.

B. Acute

Investigate agents which may be responsible for acute neurological diseases such as meningitis, encephalitis, Reye's syndrome, Bell's palsy, and tic douloureux as well as possible methods for rapid diagnosis, treatment and prevention.

C. Chronic

Study chronic neurological diseases such as multiple sclerosis, amyotrophic lateral sclerosis, progressive multifocal leukoencephalopathy, Parkinson's disease, peripheral neuropathy, polymyositis, subacute sclerosing panencephalitis, Alzheimer's and Pick's disease and epilepsy using combined tissue culture, immunological, serological, genetic, electron microscopic and clinical approaches for possible infectious etiologies. Whenever possible, explore methods for early diagnosis, treatment and prevention.

III. SECTION ACTIVITIES

A. Section on Immunochemistry and Clinical Investigations (ICI)

1. Perinatal

The Section is responsible for the research and the analysis of Collaborative Perinatal Project sera and data for infection in 60,000 pregnancies. The approaches being used include: 1) clinical infections - correlation with pregnancy outcomes; 2) serological investigation of 8,000 abnormals and 8,000 controls; and 3) high IgM among 30,000 children as a method to identify infected children. Highly sensitive ELISA tests are being applied to these studies.

Additional studies include infection in high risk children in relation to neonatal deaths and abnormal outcomes. A study is being conducted to determine the rate of herpes infections in pregnant women in several different geographic locations.

2. Acute

New tests for the detection and diagnosis of genital herpes virus infections are being perfected and evaluated in patients with this disease. The methods used employ a new biotin-avidin reaction to provide high sensitivity and specificity.

The ELISA tests are being used in studies of CSF and serum patients with a number of different neurological diseases. Group B streptococcal meningitis infections are being studied in experimental monkeys in our laboratories.

Reye's syndrome patients are being studied for viral antibody levels and aspirin tolerance.

3. Chronic

Oligoclonal IgG has been found in the CSF of patients with several different neurological diseases including MS, Epstein-Barr virus infection and myasthenia gravis. Specific tests for antibody are in progress using the new micro-oligoclonal method. Special serological investigations of MS and ALS patients are in progress.

Using a new Flow Cytofluorograph technique, studies are underway to define the immune responses in MS and other neurological diseases.

Patients with various chronic neurological diseases are being studied for virus antibodies and antigens. These diseases include: postpolio ALS, ALS, polymyositis, and peripheral neuropathy.

B. Section on Experimental Pathology (EP)

1. Perinatal

This Section is conducting studies using nonhuman primates as models to investigate the effects of *in utero* infection of several common human pathogens. Current agents include cytomegalovirus (CMV), rubella and toxoplasmosis.

2. Acute

New methods of treatment and prevention of Group B streptococcal meningitis are being studied using the monkey model developed in this Section. Acute encephalitides induced by herpes type I, the "Delta Agent," and toxoplasmosis are continuing to be investigated.

3. Chronic

Studies of subacute sclerosing panencephalitis in monkeys are in progress. Mechanisms by which the latent viral infection produced by the varicella-like "Delta Agent" can be reactivated and rescued are being studied. The neuro-oncogenic studies continue with the owl and squirrel monkey models inoculated intracerebrally with JC virus, a human polyomavirus. EAN is being studied in rhesus monkeys.

C. Section on Neurovirology (NV)

1. Perinatal

Studies are being conducted on the natural history of antibody formation to herpes infections in pregnant women. The possible role of immune complexes in influencing the initiation of the immune response in recurrent infections is being investigated. Infection of newborn rhesus monkeys with cytomegalovirus was studied to determine the pathogenesis of fetal infection. Maternal and fetal antibody responses were evaluated.

2. Acute

Studies of acute herpes infections are being conducted jointly with the Section on Immunochemistry and Clinical Investigations.

3. Chronic

Immunologic studies were continued to determine the role of immune response to viruses in multiple sclerosis. These investigations included responses to measles virus, rubella viruses, herpes simplex virus, cytomegalovirus and Epstein-Barr virus.

Studies of the pathogensis of JC virus infection in sub-human primates and humans were extended. Molecular probes were prepared and used to demonstrate JC viral DNA sequences located in tumor tissue but not in normal tissue. Structural organization, sequence and function of JC viral DNA in these tumors is under study. Antibody to JC viral and "T" antigen demonstrated a transient active viral infection preceding tumor initiation.

Differences between acute and persistent infections are being sought via use of the patas monkey - simian hemorrhagic fever virus model. Virological and immunological techniques are being used to determine the mechanism of elimination of persistent SHF virus infection by superinfection. Physical-chemical differences between acute and persistent strains of SHF virus are being investigated by monoclonal antibody and molecular biology techniques. Cellular

immunology techniques are being used to elucidate the cellular interactions involved in restricting the immune response and maintaining tolerance of persistent SHF virus infection. Immune enhancement of death is being studied in macaque monkeys.

Studies of multiple sclerosis patients are directed at the specificity of antibody in the oligoclonal bands of IgG in the CSF and to determine the specificity of antibody produced by "B" cells in the CSF.

IV. FINDINGS

A. Perinatal

1. Management of Genital Herpes During Pregnancy (ICI)

The use of weekly cultures for herpes during the last month of pregnancy was studied in 60 women with recurrent genital HSV infections. The women with positive cultures were delivered by cesarean section. All of the children were free of herpes infection.

2. Diagnostic Tests For Torch Infections (ICI)

Problems with the reliability and reproducibility of diagnostic tests for perinatal infections makes it difficult for the physician to counsel patients with these infections. Some tests are quite unreliable and should be confirmed by reference laboratories.

3. Congenital Toxoplasmosis Causes Abortion In Monkeys (EP)

Oral administration of toxoplasmosis cysts to pregnant patas monkeys resulted in abortion of the fetuses and the organisms were isolated from the products of conception.

4. Rubella Infection of Patas Monkeys Results in Infection of Fetus (EP)

Intraamniotic infection of patas monkeys at 40 days gestation resulted in chronic fetal infection and increased rates of abortion.

B. Acute

1. Herpes Infection In Pregnant Women (ICI)

A study of 210 pregnant women in Bethesda, MD showed that 25 had a history of prior genital herpes infection and 10 were shedding virus at 37 weeks gestation. This showed a high risk group for acute infection of the newborn.

2. New Biotin-Avidin Test for Genital Herpes (ICI)

A new 24 hour test for genital herpes was developed which employs tissue culture followed by a highly sensitive biotin-avidin reaction. This test has direct clinical value for the diagnosis of genital herpes.

3. IgM Serological Test for Zoster Infection (ICI)

An IgM ELISA test for IgM antibody to varicella-zoster was developed. This test is useful for the diagnosis of recent varicella or zoster infections.

4. Immunization with Live Strep B Protects Fetus from Intraamniotic Challenge (EP)

Immunization of adult rhesus monkeys with live strep B organisms resulted in protection of the fetus from group B infection when challenged intraamniotically at term.

5. PYR-Sulfa Treatment Effective for Monkeys with Toxoplasmosis (EP)

The drug PYR-Sulfa was effective in treating monkeys infected with toxoplasmosis.

C. Chronic

1. Cellular Immune Responses In Sub-Human Primates (ICI)

New markers have been developed for cell populations involved in immune responses to infections in sub-human primates. These antibodies label the cells which are then studied in a cytofluorograph. This new method makes it possible to analyze the immune responses to infection in these animals.

2. Elimination of Persistent Infection with Super Infection (NV)

Expanded studies of persistent SHF infection have shown that natural infection can be elevated by super infection with a related virus. The process clears the chronic infection and makes the animals free of infectious virus.

3. Characterization of SHF (NV)

The molecular weight of SHF virus RNA was determined to be 5.5×10^6 Daltons. The sedimentation coefficient of the RNA was found to be 49 S. The parental genome was shown to code for structural polypeptides of the virus by *in vitro* translation.

4. Immune Enhancement of Death with SHF (NV)

Infected macaques, shortly after recovery, are immune to infection and disease. If these animals are challenged several months later they experience a rapid death.

5. JC Virus Produces Glioblastomas In Second Monkey Species (EP)

The polyomavirus JC produced CNS glioblastomas in squirrel monkeys in 1½ to 2½ years. This confirmed the observations we made previously in owl monkeys.

6. Patients with Dysgammaglobulinemic Polyneuropathy have Increased Suppressor Cells (ICI)

These patients were found to have increased numbers of suppressor cells in their blood. This suggests abnormal immunoregulation. Similar findings are noted with certain viral and parasitic infections. Two of these patients have antibody to MAG. Patients with IgA polyneuropathy have an abnormal marker on the lymphocytes and IgA immune complexes.

7. ALS - PETT Scan Studies (ICI)

Patients with ALS have been studied with PETT scan and show metabolic changes although they have normal CAT scans.

8. Circulating Factors in Polymyositis Against Sarcoplasma Reticulum (ICI)

Patients with polymyositis were shown to have factors against sarcoplasma reticulum.

9. Immunocytochemical Localization of Thymosin Beta 4 (ICI)

Thymosin beta 4 was found to localize in microglial cells, certain oligodendrocytes along the long tracts, certain macrophages, and reticular-dendritic cells of lymph nodes.

10. DMSO Changes Markers of Lymphocytes (ICI)

Treatment of animals with DMSO results in surface changes of the lymphocyte markers.

11. JC Viral Genomes Detected in Brain Tumors of Monkeys (NV)

Using cloned recombinant DNA probes, JC virus DNA was found in brain tumors of monkeys.

12. Antibodies to JC Virus Found During Tumor Development in Monkeys (NV)

Antibody patterns suggest that active viral infection does not persist and after a long latent phase, viral transformation becomes evident in animals which develop JC virus induced CNS tumors.

13. Cloned Probe DNA to JC Transfected into Human Fetal Cells (NV)

Cloned JC DNA was transfected and was functionally capable of producing infectious virus in human fetal cells.

14. MS Patients Have High Levels of Several Antibodies (NV)

An increased frequency of patients with MS were found to have high levels of antibody to rubella, EB virus as well as measles.

15. Cytomegalovirus Antibody In Autoimmune Deficiency (AID) Patients Found to be Unusually High (NV)

Patients with AID had uniquely high antibody levels to CMV and not other viruses.

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal year 1982

Bio Tech Research Laboratories Inc. (NO1-NS-1-2351)

TITLE: Provide Special Tissue Culture Cells and Reagents to NINCDS

Contractor's Project Director: Dr. Anton F. Stewen

Current Annual Level: $78,333.00

Objective: This is a service contract to produce a variety of cells and reagents not available under other mechanisms for use in the research programs of the Branch.

Major Findings: A number of satisfactory lots of special tissue culture cells have been submitted to the Branch for use in our studies of the JC virus in owl monkeys and the study of herpes, CMV and rubella virus in neurological disease. Attempts to develop lymphadenoma to herpes virus have so far produced several unstable clones.

Significance to the NINCDS Program and Biomedical Research: The cells and viruses produced by this contract have been utilized in the research programs of the Branch. The reagents supplied have helped to identify the role of the "T" and "t" antigens in tumors of owl monkeys.

Proposed Course of the Project: This contract will be continued for another year.

Publications: None

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1982

Microbiological Associates (NO1-NS-9-2324)

Title: Development and Delivery of Antigen, Antisera and Viral Diagnostic Reagents.

Contractor's Project Director: Dr. Jeff Iltis

Current Funding: $482,500.00

Objectives: This is a service contract to provide reagents for the Collaborative Perinatal Research, the JC papovavirus studies and other neurological diseases.

Major Findings: A large number of high quality viral diagnostic reagents have been provided. These include antigens for Herpes viruses types I and II, Cytomegalovirus, Measles, Rubella, Influenza and Coxsackie A and B. These antigens are used in an attempt to identify the etiology of perinatal infection. Enzyme-linked immunosorbent (ELISA) tests have been developed for herpes, cytomegalovirus and measles. Some of the unexplained differences associated with plastic plates have been identified as unrecognized manufacturer changes. It has been shown that for each antigen the parameter of the test must be individually identified and standardized and that one lot of plates may not be satisfactory for another antigen. Reagents for ELISA and hemagglutination tests for the JC virus are being developed. Reagents prepared for determination of the molecular genetics of the BK and JC virus have been used successfully. Reagents to study the herpes delta agent in patas monkeys have been prepared and a new plaque variant has been identified.

Significance to the NINCDS Program and Biomedical Research: This contract provides to the Collaborative Perinatal Research Projects consistent reagents which are made under similar protocols with the same cells and strains of viruses. This allows us to test these sera for antibodies with viruses that were prevalent in 1964 -1970. Using similar production techniques, data obtained several years ago can be combined with current data. To date, over 80 publications have resulted from analyses of data from these studies. Many of the reports help establish the frequency of disease, the disease syndrome that develops and provides information on which to base rational therapeutic and preventative measures. We are well on the way to identifying the major segments of the JC virus genome. This information provides basic information as to the initiation of viral growth and may help explain the host-related mechanism of persistent infection. The experimental model for herpes zoster is needed to permit development of methods to identify people at risk and to test therapies which will modify the neurological sequelae.

Proposed Course: The contract will be continued for the next year.

Publications: Shekarchi, I.C., Sever, J.L., Tzan, N., Ley, A., Ward, L.C., Madden, D.L. Comparison of hemagglutination inhibition test and enzyme-linked immunosorbent assay for determining antibody to rubella virus. J. Clin. Microbiol. 13(5):850-854, 1981.; Iltis, J.P., Aarons, M.C., Castellano, G.A., Madden, D.L., Sever, J.L., Curfman, B.L., London, W.T. Simian varicella virus (Delta herpesvirus) infection of patas monkeys leading to pneumonia and encephalitis[1,2]. Proceedings of the Society for Experimental Biology and Medicine, 169:266-279, 1982.

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1982

Microbiological Associates: (NO1-NS-1-2386)

TITLE: Preparation and Delivery of Special Tissue Culture Cells, Media and Immunological Reagents.

Contractor's Project Director: Norma Parker

Current Level of Funding: $99,500.00

Objectives: This is a service contract to provide special tissue culture cells, media and immunological reagents for use by the Branch.

Major Findings: A large lot of pretested fetal bovine serum was obtained for use in cellular immunity studies. This lot of sera was non-stimulated to human lymphocytes. Antigens for use in the various types of cell immunity studies was grown in cells produced with this lot of fetal calf serum in order to reduce non-specific cell stimulation. Large lots of pretested microelisa plates have been obtained. Several large lots of high quality alkaline phosphatase labeled anti-human IgG or IgM have been produced which are significant to NINCDS programs and biomedical research.

Production of antigens for cell immunity studies in pretested media and use of that serum in the test itself reduces the nonspecific reactions. This allows us to determine more accurately the specific reaction. Use of specialized equipment and the knowledge of highly qualified individuals on this contract allows us to be far more flexible in purchase of equipment and hiring of personnel. Thus this contract permits us to obtain good reagents at a reasonable price and to maintain a high commitment to research on neurological disease.

Proposed Course of the Project: The contract will be continued for another year.

Publications: None

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1982

Meloy Laboratories, Inc.: (NO1-NS-7-2375)

Title: Isolated Housing and Care of Animals Used in Several Studies of Infectious Diseases.

Contractor's Project Director: Dr. John L. Cicmanec

Current Annual Level: $225,000.00

Objectives: To provide isolated housing and care of a colony of nonhuman primates consisting of several genera - example: owls Aotus trivirgatus, squirrels Saimiri sciureuis, rhesus Macaca mulatta, patas Erythrocebus patas, cynomolgus Macaca fascicularus. To provide housing and care for rodents, rabbits, guinea pigs and mice as required. The animals on experimental studies are monitored daily and biological specimens are collected as directed by written protocols.

Major Findings: This contract involves the housing and care of several species on non human primates, and several species of rodents. The animals are on various infectious disease studies. These studies involve prescreening the animals for the presence of antibody followed by inoculation of the animals by a variety of routes. The animals must then be held in strict individual isolation units. Each unit must be serviced as an individually infected area since a number of different agents are used simultaneously in the same room. Facilities for decontamination, as well as treatment of all contaminated waste and cages, must be available for the conduction of these studies.

In addition to the above, the Contract personnel under the supervision of the Contractor's Project Director, inoculates animals, monitors their health during the experiment, collect specimens as required by protocols, and perform the necropies at the termination of the experiments. Investigators on the contract must provide clinical care, with strict isolation, as well as modification of studies as necessary to achieve the overall goals of the contract.

Significance to the NINCDS Program and Biomedical Research: The goal of the NINCDS is to carry out planned, directed, research programs concerned with the diseases which damage the human nervous system. This contract provides the backup source in housing and monitoring laboratory animal models to study perinatal and neurological diseases.

Proposed Course of the Project: This Contract will be continued for the following year to provide the isolated housing and care of a colony of non human primates and rodents inoculated with various infectious agents.

Publications: None. All publications from this Contract are listed in each area of study of the Experimental Pathology Section.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-00402-26-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Perinatal Infections Causing Damage to the Child - Collaborative Perinatal Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John L. Sever	Chief	IDB, IRP, NINCDS
	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
Other:	Jonas Ellenberg	Biostatistician	OB & FS, OD, NINCDS
	Anita C. Ley	Microbiologist	IDB, IRP, NINCDS
	Nancy Tzan	Microbiologist	IDB, IRP, NINCDS
	Dorothy M. Edmonds	Clinical Nurse	IDB, IRP, NINCDS

COOPERATING UNITS (if any)

Johns Hopkins University; Univ. of CA, Los Angeles; Kaiser Hospital George Washington University Medical School; OB & FS, OD, NINCDS

LAB/BRANCH
Infectious Diseases Branch

SECTION
Immunochemistry and Clinical Investigations

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine insofar as possible the role of perinatal infections in the production of fetal damage. To accomplish this, clinical data and a large number of serial serum specimens have been obtained from the 58,000 women and their children in the Collaborative Perinatal Project. Now that the project is complete, it is possible to study perinatal infections with three main approaches: 1) clinical infections; 2) subclinical infections detected serologically using abnormals and matched controls; and 3) high risk children with elevated IgM levels. Special investigations included the epidemiology of infections and the frequency of congenital toxoplasmosis. Serum, IgM volumes, plus clinical findings are being used to identify infected infants at risk for perinatal damage. Specific tests are then applied for identification of the infection. The data indicates that congenital toxoplasmosis is rare. These studies should be completed by December, 1983.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01985-11 ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Presence of Viral and Nonviral Antigens or Antibodies in Perinatal and Neurological Diseases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
Other:	John L. Sever	Chief	IDB, IRP, NINCDS
	Aurella Krezlewicz	Microbiologist	IDB, IRP, NINCDS
	William London	Veterinary Director	IDB, IRP, NINCDS
	Maneth Gravell	Research Microbiologist	IDB, IRP, NINCDS
	William Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
	Lilly Jacob	IPA Guest Worker	IDB, IRP, NINCDS
	Lata Nerurkar	IPA Guest Worker	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
University of California, Los Angeles
Electronucleonics, Inc.
Microbiological Associates, Inc.

LAB/BRANCH
Infectious Diseases Branch

SECTION
Immunochemistry and Clinical Investigations

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	2.5	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Efforts to determine the etiological agents associated with multiple sclerosis have continued. We have completed the immunological studies using direct migration inhibition, lymphocyte cytotoxicity and complement mediated cytotoxic test and have concluded that there is no significant difference in the cellular immune responses of MS patients and carefully matched controls. Flow cytofluorometric techniques to measure the cellular immune response of lymphocytes from a number of non-human primates have been completed. Correlation of T and B lympho cyte markers as detected by monoclonal antibodies have been initiated in human and non-human primate systems. Significant alterations in the response of non-human primate lymphocytes when treated with ammonium chloride to these monoclonal antibodies have been observed. Application of the ELISA technique to measure IgG and IgM against a variety of viruses has been completed. A rapid, viral antigen diagnostic technique which reduces the time necessary to identify herpes virus in clinical specimens from 3 - 7 days to 6 - 24 hours has been developed using the avidin-biotin system. Routine monitoring of tissue cultures from experimental viral studies from mycoplasma contamination and efforts to develop new techniques to monitor cultures for contamination have been continued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-02038-10-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Combined Clinical, Viral and Immunological Investigations of Neuromuscular Diseases and Diseases of the Central Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John L. Sever	Chief	IDB, IRP, NINCDS
	Marinos C. Dalakas	Senior Staff Fellow	IDB, IRP, NINCDS
Other:	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
	Maneth Gravell	Research Microbiologist	IDB, IRP, NINCDS
	Monique Dubois-Dalcq	Research Microbiologist	IDB, IRP, NINCDS
	Giovanni DiChiro	Neuroradiologist	SNB, IRP, NINCDS
	Sidney A. Houff	Neurologist	IDB, IRP, NINCDS
	Anita Chu	Visiting Associate	IDB, IRP, NINCDS
	J. Woyciechowska	Medical Staff Fellow	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
VA Hospital, Washington, D.C.; George Washington Univ. Medical Center and Georgetown Univ. Medical School, Washington, D.C.; Children's Hospital, Washington, D.C.; National Naval Medical Center (NNMC), Bethesda, MD

LAB/BRANCH
Infectious Diseases Branch

SECTION
Immunochemistry and Clinical Investigations

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	1.5	3.0

CHECK APPROPRIATE BOX(ES)

☒(a) HUMAN SUBJECTS ☒(b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
Clinical and laboratory studies are conducted to determine etiology (infection, immunity and/or genetics) for chronic diseases of the peripheral and central nervous system. Current studies include amyotrophic lateral sclerosis, (ALS), polymyositis/dermatomyositis, demyelinating polyneuropathies and chronic Guillain-Barre syndrome, Reye's syndrome, multiple sclerosis, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis and myasthenia gravis. Combined clinical data, genetic information, HLA and MLC typing virus serology and virus isolation studies are obtained for these studies. The nature of oligoclonal bands found in the CSF of patients with chronic neurological diseases is under investigation. A new neuromuscular disease that occurs in patients who have had poliomyelitis at an early age has been clinically defined; the possiblity that this might be due to a late or slow polio virus infection or an immune reaction to it is under investigation. Abnormal immunoregulation has been recognized in patients with paraproteinemic polyneuropathies. In patients with hereditary neuropathy and elevated IgA, abnormal phenotypic markers on B lymphocytes and IgA immune complexes have been identified.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-01731-14-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Isolation, Characterization and Diagnosis of Infectious Agents from Chronic Diseases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Maneth Gravell	Research Microbiologist	IDB, IRP, NINCDS
Other:	William T. London	Veterinary Director	IDB, IRP, NINCDS
	Marta Monzon	Guest Worker	IDB, IRP, NINCDS
	Jose Luis Sagripanti	Visiting Fellow	IDB, IRP, NINCDS
	Rebecca S. Hamilton	Biologist	IDB, IRP, NINCDS
	Otto Gutenson	Biologist	IDB, IRP, NINCDS
	Blanche Curfman	Biologist	IDB, IRP, NINCDS
	Robert Brown	Biological Lab Tech	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
Section on Experimental Pathology, IDB, NINCDS

LAB/BRANCH
Infectious Diseases Branch

SECTION
Neurovirology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.6	2.4	2.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Macaque monkeys undergoing primary infection with simian hemorrhagic fever (SHF) virus develop an acute, febrile hemorrhagic disease and generally die 5 to 14 days after infected. Occasionally, infected macaques completely recover from infection. Animals infected 6 months or more after recovery with homotypic or heterotypic strains of SHF virus died more rapidly (<2 days) than primarily infected animals. At the time of second infection, high serum antibody titers to viral antigens were detected, but this antibody lacked neutralizing activity. Antibody did not appear to be the cause of the more rapid death because macaques receiving passively transferred specific viral antibody did not die any more rapidly than primarily infected animals. These results suggest that vaccination of macaques with SHF virus would afford short lived protection and, in fact, could exacerbate subsequent SHF virus infections. Many of the physical-chemical characteristics of SHF virus, a member of the Togaviridae family, have not been determined. We have found the genome of SHF virus to be a single linear positive stranded molecule of RNA (Mol. Wt. 5.5×10^6 daltons, sedimentation coefficient 49S). SHF virions contain 5 polypeptides ranging in Mol. Wt. from 50K to 10K daltons.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-NS-01983-11-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Chronic Viral Infections

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William C. Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
Other:	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
	John L. Sever	Chief	IDB, IRP, NINCDS
	William T. London	Veterinary Director	IDB, IRP, NINCDS
	Sidney A. Houff	Clinical Associate	IDB, IRP, NINCDS
	Renee G. Traub	Microbiologist	IDB, IRP, NINCDS
	Nancy Miller	Expert Consultant	IDB, IRP, NINCDS
	Eugene Major	IPA	IDB, IRP, NINCDS
	Norma Witzel	Microbiologist	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
Microbiological Associates, Bethesda, MD; Loyola Univ., Maywood, IL; George Washington Univ. Medical School, Washington, DC; Veterans Admin. Hospital, Washington, DC; Georgetown Univ. Medical Center, Washington, DC

LAB/BRANCH
Infectious Diseases Branch

SECTION
Neurovirology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.8	0.8	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In studies on chronic central nervous system diseases, markers for tumor involvement in the CNS of patients with Burkitt's lymphoma were described. Elevated antibodies to Epstein-Barr virus, myelin, basic protein and cerebroside were detected. Oligoclonal IgG was demonstrated and immune complexes were found in CSF of these patients. Immunoregulatory deficiencies were potentially described in homosexual males who heavily used amyl nitrite.

In studies of patients with multiple sclerosis, immune complex levels were found to vary with disease exacerbation in MS patients but antibody levels to several viruses were shown to remain unchanged.

In studies regarding JC virus pathogenesis, JC virus DNA was demonstrated in brain tumors and tumor cell lines from owl monkeys inoculated with JC virus. Cloned JCV DNA was transfected into oligodendroglial cells and infectious virus was recovered.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-NS-01984-11-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Maternal Infection and Pregnancy Outcome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William C. Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
Other:	John L. Sever	Chief	IDB, IRP, NINCDS
	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
	William T. London	Veterinary Director	IDB, IRP, NINCDS
	John H. Grossman	Guest Worker	IDB, IRP, NINCDS
	Frank J. West	Bio Lab Technician	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
George Washington University Medical School, Washington, D.C.

LAB/BRANCH
Infectious Diseases Branch

SECTION
Neurovirology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.2	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The natural history and immune response of women with HSV infections were studied. Most virus isolates from 50 pregnant women were serotyped as HSV-II or very similar to HSV-II. None of the isolates typed as HSV-I. Antibody to HSV-II as measured by neutralization or by indirect hemadsorption tended to rise early but did not correspond with clinical symptoms while cytotoxic antibody arose later and tended to correspond better with clinical symptoms.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-02531-01-ID

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Immunological, Histological and Immunocytochemical Studies in Neuromuscular and Central Nervous System Diseases and Investigations of their Experimental Models

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John L. Sever	Chief	IDB, IRP, NINCDS
	Marinos C. Dalakas	Senior Staff Fellow	IDB, IRP, NINCDS
Other:	David L. Madden	Veterinary Director	IDB, IRP, NINCDS
	Maneth Gravell	Research Microbiologist	IDB, IRP, NINCDS
	Monique Dubois-Dalcq	Research Microbiologist	IDB, IRP, NINCDS
	William T. London	Veterinary Director	IDB, IRP, NINCDS
	Bruce Trapp	Microbiologist	IDB, IRP, NINCDS
	Richard Quarles	Biochemist	DMN, IRP, NINCDS
	M. Gelfand	Associate Professor	Georgetown University
	Allan Goldstein	Professor and Chairman	George Washington U.
	H. Costa	Pathologist	Clinical Center, NIH

COOPERATING UNITS (if any)

VA Hospital, Washington, D.C.; George Washington University Medical Center and Georgetown University Medical School, Washington, D.C.; Children's Hospital, Washington, D.C.; National Naval Medical Center (NNMC), Bethesda, MD

LAB/BRANCH

Infectious Diseases Branch

SECTION

Immunochemistry and Clinical Investigations

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	1.5	3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Enzyme histochemistry in muscle and nerve biopsies is carried out for diagnostic purposes in patients with several neuromuscular disorders. Immunocytochemical studies are conducted using specific antibodies to thymic peptides, to investigate changes in the distribution of epithelial cells and thymocytes in the thymus of patients with myasthenia gravis. Using the cytofluorograph, specific subsets of lymphocytes that carry thymic markers are now being defined. The immunoglobulin of certain patients with paraproteinemic polyneuropathies has been identified as a specific antibody to myelin associated glycoprotein; nerve biopsies from these patients are studied by electron microscopy and immunocytochemically with specific antimyelin antibodies. Serum from patients with demyelinating polyneuropathies is tested in cultures of human Schwann cells for cytotoxicity and specific binding. Because muscle and nerves are involved in antigen-antibody immune reactions, the presence of Fc receptors for IgG and complement in fresh muscle and nerve tissues is being examined. Immune cellular markers during evolution of EAN and EAE induced in monkeys are being investigated and therapies are planned using some novel immunomodulating agents.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 00972-11 ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Role of Viruses and Other Microorganisms in the Perinatal Period of Experimental Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William T. London	Veterinary Director	IDB, IRP, NINCDS
	James S. Harper, III	Veterinary Medical Officer	IDB, IRP, NINCDS
Other:	John L. Sever	Chief	IDB, IRP, NINCDS
	William C. Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
	Blanche L. Curfman	Biologist	IDB, IRP, NINCDS
	Robert L. Brown	Biological Lab Technician	IDB, IRP, NINCDS
	Frank J. West	Biological Lab Technician	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
University of Pittsburgh Presbyterian Hospital, Department of Neuropathology, Pittsburgh, Pennsylvania
Meloy Laboratories, Inc., Springfield, Virginia

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.3	0.5	1.8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Congenital Toxoplasmosis: Erythrocebus patas is the monkey most suitable for studies of acquired toxoplasmosis. They are readily infected by oral administration of toxoplasma cysts. The infection in this monkey closely resembles that in humans. The animals become ill for several days, then as antibody develops they gradually recover. A dosage that will infect the pregnant animal and not invariably result in abortion is being determined.

Rubella Virus: Rubella virus produces congenital infection in the patas monkey. The virus was isolated from various fetal tissues 77 to 120 days after intra-amniotic inoculation into pregnant patas monkeys at 40 days gestation. This presents an opportunity to study the pathogenesis of this important human teratogen.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01986-11 ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Inoculation of Animals with Tissue Culture Grown Materials from Patients with Chronic Neurologic Diseases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William T. London	Veterinary Director	IDB, IRP, NINCDS
Other:	Marinos C. Dalakas	Senior Staff Fellow	IDB, IRP, NINCDS
	John L. Sever	Chief	IDB, IRP, NINCDS
	Blanche L. Curfman	Biologist	IDB, IRP, NINCDS
	Robert L. Brown	Biological Lab Technician	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
Meloy Laboratories, Springfield, Virginia
Microbiological Associates, Bethesda, Maryland

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	0.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Delta herpesvirus infection in Erythrocebus patas monkeys - A model for human herpes zoster complications: Experimental studies have indicated that patas monkeys become persistently infected with Delta herpesvirus (DHV). We are investigating how to activate this persistent infection in the monkey model.

Experimental allergic polyneuritis (EAN) in rhesus monkeys: Although cellular immune mechanisms are thought to be responsible for the development of EAN, the immunoregulatory mechanisms and participation of specific lymphocyte subsets in antigen recognition and demyelination during evolution of EAN are now known. We are serially recording lymphocytes during the development of EAN in rhesus monkeys using mouse monoclonal antibodies that recognize membrane markers of different lymphocyte subpopulations.

Subacute sclerosing panencephalitis (SSPE): Young cynomolgus monkeys Macaca fasiculorus that were inoculated with "Biken" strain of measles virus (SSPE) have been monitored for clinical signs of disease. This is a long term project and signs of disease are not expected until 24 - 30 months post inoculation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02136-08 ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Control of Acute Infectious Diseases in Experimental Animals Using Biologicals and Chemotherapeutic Agents

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William T. London	Veterinary Director	IDB, IRP, NINCDS
	James S. Harper III	Veterinary Medical Officer	IDB, IRP, NINCDS
Other:	John L. Sever	Medical Director, Chief	IDB, IRP, NINCDS
	William C. Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
	Blanche L. Curfman	Biologist	IDB, IRP, NINCDS
	Robert L. Brown	Biological Lab Technician	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
Meloy Laboratories, Inc., Springfield, Virginia
Microbiological Associates, Bethesda, Maryland

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.2	0.7	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A major question in the prevention of group B Streptococcus type III (GBS) meningitis in humans is the efficacy of vaccination. Killed vaccines have not elicited good immune responses in both animal and human test groups. We have asked the question: "Will maternal immunization with live organisms prevent disease in offspring following in-utero challenge 24 hours before delivery?". Preliminary data indicate that vaccination with live organisms is efficacious in the rhesus monkey model.

Several drug regimens were compared in the squirrel monkey model for the treatment of acute toxoplasmosis. The combination of pyrimethamine/sulfadiazine (PYR/SLD) or trimethoprim/sulfamethoxazole (TMP/SMZ) were equally effective in treating toxoplasmosis in the monkey model. TMP has been associated with fewer human toxic side effects than PYR. TMP has also been used in pregnant women without demonstrated teratogenic effect. It is available in an intravenous solution so that therapeutic blood levels can be quickly achieved. Controlled human studies of the use of TMP/SMZ in acute toxoplasmosis may be indicated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-NS-02271-06-ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Papovaviruses in Non-human Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William T. London	Veterinary Director	IDB, IRP, NINCDS
	Sidney A. Houff	Research Associate	IDB, IRP, NINCDS
Other:	William C. Wallen	Senior Staff Fellow	IDB, IRP, NINCDS
	John L. Sever	Chief	IDB, IRP, NINCDS
	Giovanni Di Chiro	Chief	NCT, SNB,NINCDS
	Nicholas J. Petronis	Medical Officer	NCT, SNB,NINCDS
	Ronald G. Blasberg	Senior Investigator	DTP, DCT, NCI
	Paul E. McKeever	Medical Officer	SNB, NINCDS
	Blanche L. Curfman	Biologist	IDB, IRP, NINCDS
	Robert L. Brown	Biological Lab. Technician	IDB, IRP, NINCDS

COOPERATING UNITS (if any)
University of Wisconsin Medical School, Departments of Medical Microbiology and Pathology, Madison, Wisconsin; SNB, NINCDS
Meloy Laboratories, Inc., Springfield, Virginia

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	0.3	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Eighteen owl monkeys (Aotus trivirgatus) and four squirrel monkeys (Saimiri sciureus) developed intracerebral gliomas that were predominantly astrocytic in cell type. This is the completion of the studies using 92 owl monkeys and 15 squirrel monkeys that were inoculated in 1978 with JC virus, a human polyomavirus or control material. The monkeys were monitored for 36 months (August, 1981) before the studies were terminated.

Additional owl and squirrel monkeys were inoculated with JC virus or control material. Animals developing intracerebral tumors from this group of monkeys will be studied using positron emission tomography or autoradiography. Some of the tumor material from the monkeys will be used to complete hybridization studies between JC virus DNA and DNA extracted from tumor cells to delineate portions of JC virus DNA present in the tumor genome.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02034-10 ID

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Electron Microscopic Studies: Viruses of the Nervous System and Demyelination

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dr. Monique Dubois-Dalcq	Research Microbiologist	*LMG, IRP, NINCDS
Other:	Dr. B. Trapp	Senior Staff Fellow	*LMG, IRP, NINCDS
	Dr. R. Nick Hogan	Senior Staff Fellow	*LMG, IRP, NINCDS
	Dr. S. Ohno	Fogarty Postdoctoral Fellow	*LMG, IRP, NINCDS
	R. Rusten	Biological Lab Technician	*LMG, IRP, NINCDS
	S. Schmidt	Microbiologist	*LMG, IRP, NINCDS
	A. Baron	Ph.D. Student	*LMG, IRP, NINCDS
Collaborators:	Dr. R. Quarles	Chief, Section on Myelin & Brain Development	DMN, IRP, NINCDS
	Dr. M. Dalakas	Senior Staff Fellow	IDB, IRP, NINCDS
	Dr. K. Ramohan	Clinical Associate	NIB, IRP, NINCDS
	Dr. H. Arnheiter	Guest Worker	LMG, IRP, NINCDS

COOPERATING UNITS (if any)
Dr. J. Griffin, Department of Neurology, Johns Hopkins University School of Medicine; Dr. J. Ochoa, Department of Neurology, Dartmouth Medical School.

LAB/BRANCH Infectious Diseases Branch
[*Transferred to Laboratory of Molecular Genetics (4/1/82)]. *Formerly with IDB.

SECTION
Electron Microscopy Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5.7	2.7	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A. Human sensory ganglia and spinal cord of fetal origin are cultured and characterized using nerve cell specific markers and autoradiography. Neurite growth of postmitotic sensory neurons is enhanced specifically by mouse nerve growth factor (NGF) and the adhesion molecules laminin and fibronectin. Synergism between NGF and laminin results in a three-fold increase of neurite length. B. Neurotropic viruses: human fetal spinal cord cultures infected with measles virus develop extensive fusion and virus production in non-neuronal (NN) cells while neurons do not show infection until much later. Addition of antiviral antibodies to the cultures results in prolonged infection of NN cells with sparing of neurons. Viral assembly of a rhabdovirus is studied with monoclonal antibodies to 3 viral proteins: the glycoprotein G, the membrane protein M, and the nucleocapsid protein N, and each of them display different intracellular. C. Immunocytochemical studies of peripheral myelin: P_2 protein is located throughout Schwann cell cytoplasm and at the major dense line of compact myelin and myelin associated glycoprotein plays a role in maintaining periaxonal space. Sural nerve biopsies from paraproteinemia patients with neuropathy show axonal and not demyelinating lesions.

TAB 21 -- MEDICAL NEUROLOGY BRANCH -- MNB/IRP

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Medical Neurology Branch

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 to September 30, 1982
Medical Neurology Branch
National Institute of Neurological and
Communicative Disorders and Stroke

The Medical Neurology Branch conducted no research activities during the past year and has now been discontinued.

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Neuroimmunology Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
October 1, 1981 to September 30, 1982
Neuroimmunology Branch
National Institute of Neurological and
Communicative Disorders and Stroke

Dale E. McFarlin, M.D., Chief

Research in the Neuroimmunology Branch (NIB) is directed at assessment of immune mechanisms operative in neurological diseases. These investigations include studies of both experimental diseases in animals and human diseases which may have an immunological basis. Over the last year emphasis has been given to three general areas. First, the interactions of immunologically competent cells have been studied extensively in both experimental models and man. These investigations have been facilitated by the use of monoclonal antibodies in conjunction with cell sorting technology. Secondly, attention has been focused on the characterization of antigens which are the targets of the immune response. Monoclonal antibodies have also contributed significantly to the progress of this work. Thirdly, in the design and execution of our studies, considerable attention is being given to genetic factors which are linked to regulation of the immune response.

Studies on experimental allergic encephalomyelitis (EAE) have focused on the production of this disease in mice because many of the fundamental principles of basic immunology have been established in this species. Our laboratory has pioneered in the reproducible induction of this autoimmune disease in mice which should facilitate the analysis of the underlying mechanisms. Three different types of murine EAE have been produced. Each has merit in addressing specific immunological questions. Chronic relapsing EAE has been systematically evaluated pathologically. Over a six month period as many as six clinical episodes were documented in some mice; these correlated pathologically with multiple lesions of different ages. The central nervous system changes included hemorrhages and significant nerve fiber depletion during the early stages of the disease as well as primary demyelination. These were followed by remyelination, gliosis and invasion of the central nervous system by Schwann cells which were active in myelination. These processes seemed to recur with each acute episode. It is anticipated that this model will have widespread application in investigation of pharmacological and immunological manipulations which modify the disease. Acute EAE produced in response to myelin basic protein can be adoptively transferred to normal syngeneic recipients. This has permitted characterization of the immunological cells involved in the transfer process. It was found that the active cells belonged to a particular set of thymus-derived lymphocytes which are Lyt $1+2^-$. The biological and pharmacological properties of these cells are distinct from the other major subset of murine thymus-derived lymphocytes. These studies have been extended to initiate characterization of the antigenic determinants responsible for the murine disease. The long-term goal of the studies is to understand the pathogenesis and the immunoregulatory processes which, when modified, result in disease.

Subsets of peripheral blood lymphocytes are also being extensively studied. Most of our studies are being performed with the OKT series of markers. The OKT3 antiserum identifies approximately 95% of T-cells in the peripheral blood while the OKT4 and OKT8 reagents identify subpopulations with helper-inducer and suppressor/killer functions respectively. Normal values for these lymphocyte phenotypes in the peripheral blood have been established and these are currently being measured in our patients. Although reduced numbers of lymphocytes bearing the OKT8 marker have been seen in some patients with multiple sclerosis, in our experience this occurs in a much smaller percentage of patients than reported by other laboratories. Further, the majority of patients with active multiple sclerosis have normal peripheral blood phenotypes. Because disease activity may be related to abnormalities in the peripheral blood lymphocyte subsets, a longitudinal study of a few patients is being conducted. In addition, focus is being placed on the cellular immune response to specific antigens. The cellular immune response to both influenza and measles viruses have been studied extensively. Detailed analysis of the cellular response to measles has been conducted in identical twins who are discordant for multiple sclerosis and who differ in the response to this virus as measured by lymphocyte proliferation. The responding cells are $OKT3^{+}4^{+}8^{-}$ and require antigen presenting cells. Because most normal individuals are relatively low responders to measles virus as measured by the lymphocyte proliferative assay, a defect in suppressor lymphocytes has been postulated in the individuals with multiple sclerosis who are high responders. Extensive studies have not identified such cells. A different subset of human T cells is responsible for mediating a cytotoxic response against influenza infected cells. These effector cells are $OKT3^{+}4^{-}8^{+}$. In order to generate these cytotoxic cells, antigen presenting cells and another subset of activated T cells, $OKT3^{+}4^{+}8^{-}$ are required. These studies of cellular immunity against viruses indicate that the various T cell subpopulations react with different types of antigenic targets. The $OKT3^{+}4^{-}8^{+}$ cells which are cytotoxic to influenza infected targets require antigen presented in the presence of HLA-A or -B identical targets. However, the proliferation of $OKT3^{+}4^{+}8^{-}$ cells can be obtained with both HLA identical and HLA nonidentical measles infected fibroblasts. It is likely that these lymphocytes respond to antigen presented on macrophages in the presence of DR antigens and produce a variety of soluble substances such as interferon and interleukin-2. Such cellular interactions are being analyzed with T-cell clones directed at viral determinants.

Studies on the antigenic determinants which are the targets of the immune response have progressed. Because measles virus is highly cell associated and does not turn off synthesis of host proteins, in the past, it has been extremely difficult to study the production of antigens encoded for by this virus. Monoclonal antibodies against individual components of measles virus have made it possible to overcome these technical problems. These investigations have focused on the HA protein, a glycoprotein which is expressed on the surface of the virus. The biosynthesis, transport and insertion of this important antigen in infected cells has been characterized in considerable detail. Not only is this work important, per se, but in addition it provides background and insight for the use of monoclonal antibodies to study trace substances in normal and infected cells.

Variation in the HA antigen among various strains of measles virus has been documented. This is particularly relevant because the hampster neurotropic strain (HNT) tends to have different antigenic determinants than some of the more common strains of the virus. Previously, our laboratory demonstrated that mice which are infected with the HNT strain of measles virus become acutely ill and die. However, if the infected mice are given hyperimmune anti-measles antibody three days after inoculation of virus, the animals do not develop the acute disease, and a significant proportion of the survivors develop a chronic neurological condition. It was subsequently shown that one of the monoclonal antibodies against the HA protein produced similar effects. Further, it is of considerable interest that this phenomenon was not obtained with all monoclonal antibodies which react with the HA protein of the Edmonston strain of measles. Our data indicate that some of the antigenic determinants present on the Edmonston strain of virus are not expressed in the neurotropic strain. These observations suggest that changes in viral antigen are related to neurotropism. This possibility will be the focus of additional studies.

As part of our effort to understand immunoregulatory mechanisms operative during infection, the role of idiotypes and anti-idiotypes in the immune response to the measles HA protein have been studied. Syngeneic anti-idiotypes against monoclonal antibodies directed at the HA protein were produced. The anti-idiotypes blocked the biological function of the monoclonal anti-HA antibodies. Search for a major dominant cross-reacting idiotype in the sera of hyperimmunized animals was conducted. Although some limited cross-reactivity was encountered with one of the anti-idiotypes, a predominant cross-reactive idiotype was not detected. Since auto anti-idiotypes significantly interfere with the biological effect of the idiotypic bearing molecules or possibly immunologically competent cells, it is our belief that idiotypic heterogeneity is a beneficial component of an anti-viral immune response.

As noted above, cytotoxic T cells directed at influenza virus recognize this infectious agent in conjunction with HLA-A and -B gene products. Thus, the histocompatibility antigens on the surface of the infected target cell control the capacity of lymphocytes to recognize the viral antigen. Studies of this problem have identified individuals who carry variant HLA-A2 and HLA-A3 molecules. These variants lack one or more of the epitopes necessary for recognition of virus infected targets by cytotoxic lymphocytes. Biochemical analysis of these variant HLA molecules is in progress and the preliminary results indicate that at least two discrete sites on the HLA-A2 molecule control the interaction between lymphocytes and infected targets.

Over the last year, the clinical activities of the Neuroimmunology Branch have been expanded. In addition to the studies of immune regulation in multiple sclerosis, a new protocol involving assessment of immune function in myasthenia gravis and three therapeutic trials of a preliminary nature in patients with multiple sclerosis have been initiated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02202-07 NI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Immunological Studies in Patients with Multiple Sclerosis and Other CNS Diseases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.E. McFarlin	Chief	NI	NINCDS
	H.F. McFarland	Asst. Chief	NI	NINCDS
OTHER:	K.W. Rammohan	Sr. Staff Fellow	NI	NINCDS
	J.I. Greenstein	Sr. Staff Fellow	NI	NINCDS
	J.W. Rose	Med. Staff Fellow	NI	NINCDS
	W.E. Biddison	Sr. Staff Fellow	NI	NINCDS
	C.T. Bever	Med. Staff Fellow	NI	NINCDS
	X.H. Xu	Guest Worker	NI	NINCDS

COOPERATING UNITS (if any)
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NES, ODIR, NINCDS

LAB/BRANCH
Neuroimmunology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5.0	3.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The general aim of this project is to obtain a more precise understanding of multiple immunological and genetic factors possibly related singly or in combination to the pathogenesis of multiple sclerosis. These include: (1) Determination of histocompatibility types in a carefully selected population of MS patients and appropriate controls. (2) Correlation of histocompatibility data with the humoral and cell-mediated immune response to viruses. (3) Identification of new lymphocyte antigens which may show greater correlation with multiple sclerosis than presently identified lymphocyte antigens. (4) Evaluation of cerebrospinal fluid immunoglobulin content and specificity. (5) Evaluation of families with a multiple incidence of multiple sclerosis and examination of affected and nonaffected members of these families with respect to the above. To minimize some of the variables in the disease, identical and nonidentical twins who are either discordant or concordant for MS are being studied. (6) Similar studies are being conducted in patients with SSPE, myasthenia gravis and other neuromuscular diseases.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02203-07 NI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Immune Response Against Membrane Antigens

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to characterize the immune response to virus components and other antigens expressed on the surface of infected cells. The function of histocompatibility antigens in forming the target of the immune response is being assessed. Monoclonal antibodies to a major surface component of measles virus, the hemagglutinin, have been produced and used to characterize the biosynthesis, glycosylation and insertion of this protein. Syngeneic anti-idiotypic antibodies directed at monoclonal anti-hemagglutinin antibodies have been produced and are being used to seek major cross-reactive idiotypes. The interaction between anti-idiotypes and the anti-viral immune response is being investigated as well as the regulation of individual idiotypes.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02204-07 NI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Immunologic Mechanisms Operative in Experimental Autoimmune Diseases of the Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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LAB/BRANCH
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SECTION
Neurological Diseases Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The aim of this project is to identify the relative role of various mechanisms operative in the production of experimental allergic encephalomyelitis, a model of autoimmune disease which is manifested by demyelination. Focus is being placed on the production of this disease in mice because this species is ideally suited for the analysis of immunologic and genetic factors which lead to disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02205-07 NI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Interaction Between Viruses and the Host Immune-System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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	K.W. Rammohan	Clinical Assoc.	NI	NINCDS
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COOPERATING UNITS (if any)

LMB, NINCDS
ID, NINCDS

LAB/BRANCH
Neuroimmunology

SECTION
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INSTITUTE AND LOCATION
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to examine the host immune response to viruses which can produce either acute or chronic infections of the CNS. These studies will examine the host immune response and its relationship to mechanisms of protection as well as disease production. In addition, attention will be directed at the immune response to viruses in order to permit identification of disease associated abnormalities.

TAB 23 -- SURGICAL NEUROLOGY BRANCH -- SNB/IRP

ANNUAL REPORT
October 1, 1981 through September 30, 1982

Surgical Neurology Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1981 through September 30, 1982
Surgical Neurology Branch, IRP
National Institute of Neurological and Communicative Disorders and Stroke

Paul L. Kornblith, M.D., Chief

Summary of Studies in the Surgical Neurology Branch

This annual report is the fourth of the Surgical Neurology Branch beginning October 1, 1981 under the leadership of Dr. Paul Kornblith. The Branch has continued to mature and become increasingly productive in its mission of the conduct of basic and clinical research on brain tumors. Reorganization of the Branch including the reequipping and redesign of of all laboratory facilities is complete and the tissue culture, electron microscopy and quantitative image analysis, neuropathology, humoral immunology, cellular immunology, metabolism and neurochemistry, positron emission tomography, and differentiation/monoclonal antibody modules are all functioning.

Addition of scientific personnel to work in each of these areas has included:

Dr. Joseph Bressler - cell differentiation - monoclonal antibody (1982)
Dr. Craig Cummins - metabolism and neurochemistry (1981)
Dr. Maurice Gately - cellular immunology (1979)
Dr. Paul McKeever - neuropathology and cell biology (1979)

Senior clinical personnel, in addition to Drs. Kornblith and Smith include:

Dr. Conrad Kufta
Dr. Edward Oldfield
Dr. Raymond Sawaya
Dr. Donald Wright (EOD 7/1/82)

To be added are additional scientific personnel in the areas of cellular and humoral immunology and electron microscopy/image analysis.

The primary areas of our research activities have included:

1. Biological, immunological and chemotherapeutic studies in human brain tumors.
2. Biological studies of human pituitary tumors.
3. Neurodiagnostic studies including the PET scan.
4. Neurophysiological studies.

The Clinical Service now has 14 beds on both 5E and 5W as well as operating facilities in Building 10A. More than 100 major neurosurgical cases will be done this year. Clinical admissions are close to 150 per year with consultations for other Institutes at NIH numbering approximately 80/year. Two clinics are functional with more than 700 clinic visits per year. The SNB, through Dr. McKeever, now provides a neuropathology service to the NIH. Ten clinical protocols for brain tumor patients are currently in effect. These are:

1. Evaluation of Biological, Immunological and Chemotherapeutic Parameters in Brain Tumor Patients.
   Project No. 79-N-89

2. Immunotherapy of Malignant Brain Tumors
   Project No. 70-N-133

3. Biological Studies of Human Pituitary Tumors
   Project No. 79-N-151

4. Evaluation of Thrombo-embolic Complications in Brain Tumor Patients Using ^{125}I-Fibrinogen Scanning
   Project No. 82-N-23

5. Evaluation of Biological, Immunological and Chemotherapeutic Parameters in Patients with Non-Astrocytic Central Nervous System Tumors
   Project No. 82-N-25

6. Selective Intra-Arterial Chemotherapy in the Treatment of Recurrent Malignant Brain Tumors
   Project No. 82-N-41

7. ^{18}F-2-Fluoro-2-deoxy-D-glucose (FDG) Positron Emission Computed Tomography (PECT) in Typing of Cerebral Gliomas
   Project No. 80-N-36

8. Use of Argon Laser for Surgical Excision of Brain, Spinal Cord, and Pituitary Tumors
   Project No. 81-N-181

9. A Phase I Study of Bromodeoxyuridine (NSC 38297) Given by Peripheral Venous Infusion

10. Phase II Trial of AZQ in Patients with Malignant Glioma and Metastatic Brain Tumors

11. Phase I Trial of CBDCA

12. Prospective in vitro Selection of Chemotherapy Agents for Patients with Malignant Brain Tumors

In collaboration with NCI

The clinical neurosurgical service includes formal rounds twice a week, a yearly sequence of neuroscience, neuro-oncology, and neurochemistry courses for junior and senior clinical staff as well as a weekly neurosurgical journal review, a weekly neuropathology conference and a biweekly neuroradiology conference. In addition, the SNB takes an active part in the weekly NINCDS Grand Rounds.

The sequence of protocols developed over the past three years, covers each of the major present or potential treatment modalities for brain tumors. This year, for surgery, the argon laser has been introduced to attempt to improve surgical resection. Rapid frozen section glial fibrillary acidic protein and fibronectin staining have been implemented to provide more accurate intraoperative neuropathological diagnostic techniques (Dr. McKeever and co-workers). For radiation therapy, we have added the use of a radiation sensitizer (BUdR) to enhance the benefits of radiation therapy, in collaboration with Dr. Glatstein of the National Cancer Institute. With intravenous administration, it is now possible for patients to administer the drug to themselves outside the hospital via special pump devices and new externalized catheter systems. To date, eleven patients have received BUdR as an adjunct to their radiation therapy and we are in the process of collecting survival data.

For clinical chemotherapy we have been able to add two new drugs to the antiglioma armamentarium - AZQ (aziridinylbenzoquinone) and "chocolate" or CBDCA platinum. AZQ is now in Phase II testing with some 20 patients having received the drug. CBDCA platinum is now in early Phase I testing.

Selective intraarterial BCNU therapy has also been instituted. This method of drug delivery, most suitable for patients in whom the main vascular tumor supply is via the anterior or middle cerebral artery, permits the delivery of up to five times the dose delivered by the intravenous route without apparent increase in the bone marrow toxicity of the BCNU. Such elevated BCNU levels should increase overall tumor response to the nitrosourea since in vitro microcytotoxicity data indicate that many cell lines resistant at normally-achieved intravenous levels are sensitive at the higher concentrations achieved by intraarterial drug delivery.

Tumors available for in vitro study now number well over 100 each year and include glial as well as other types of central nervous system tumors. Cooperating centers include Walter Reed Army Medical Center, George Washington University, Georgetown University, Childrens' Hospital (Washington, DC) and a variety of other centers scattered around the country.

Over the period of this report, over one hundred surgical cases have been done, which have provided new tumor material for study. Major upgrading of the surgical facilities has been ongoing and has included the testing of an argon laser and a cavitron. Metabolic studies of patients with brain tumors have continued. Studies in over 70 patients with the positron emission tomographic scanner have shown a relationship between glucose uptake and degree of tumor growth.

1. BIOLOGICAL, IMMUNOLOGICAL AND CHEMOTHERAPEUTIC STUDIES IN HUMAN BRAIN TUMORS

A. Biological Characterization and Neuropathological Studies

A major fact emerging from cell biological as well as chemotherapy studies in the Surgical Neurology Branch has been that of the diversity of glioma cell populations. This heterogeneity has been found not only for tumors of the same pathological grade, but also within the cell populations of a single tumor. While the biological origins of this diversity are not as yet clear, the therapeutic significance of such facts makes individualized glial tumor study critical to further clinical and basic research progress. The tissue culture of human brain tumor cells obtained at surgery offers the opportunity for both improved understanding of the cell biology of these tumor cells and the individualization and, thereby, optimization of brain tumor therapy.

A variety of morphological, cell biological and biochemical parameters are relevant to the characterization of glial tumor cells. For example, from a morphological point of view, surface membrane, nuclear, and cytoplasmic features have long been felt to be useful in the evaluation of malignancy in tumor cells at both the light and electron microscopic levels. Evident with experience with any one characterization modality are the limitations of "static" evaluations. Morphologic features of extensive surface microvilli, dilated endoplasmic reticulum, and bizarre, multilobular nuclei are, in themselves, indicators of limited value in determining the dynamic response characteristics of any given malignant cell, just as static metabolic measurements of anaerobic or oxidative metabolism, cytogenetic analyses, or even cell kinetics may tell only a part of the tumor cell's biology. No one "static" approach to glial tumor cell characterization is likely to lead to significant advances in understanding malignant cell behavior. Needed are "dynamic" behavioral characteristics of tumor cells to which a multimodal analytical, biophysical and biochemical approach can be applied. Utilizing these approaches it has been possible to show that certain characteristics of cultured human brain tumor cells not only parallel those of the cells in a patient but also provide the opportunity to add therapeutically relevant information to the planning of optimal therapy and the prediction of the way in which a tumor will grow in a given patient. This type of work has two major areas. First is the area of the prediction of the behavior of tumors which are known to be malignant. Here the major question is how malignant a given tumor will be. Secondly, in certain tumors, which by and large are benign or nonmalignant in their growth, there are occasional instances in which tumors do grow in a malignant fashion. In the second category, the question is how to pick out ahead of time those tumors which behave in a malignant or invasive fashion. These are the two primary goals of the program in the study of tumor biology. There are, in addition, several secondary goals. These include: studies of the basic biologic mechanisms of tumor growth and the similarities and differences of this tumor growth to the growth of normal cells.

The observations made in our laboratory that glial and other central nervous system tumor cells vary in their sensitivity to the nitrosourea BCNU as well as aziridinylbenzoquinone (AZQ) and cis-platinum have provided cellular response phenomenology suitable for a dynamic analysis as described above. In other words, the response of glial tumor cells to given chemotherapeutic (cytotoxic) agents as well as biological growth regulatory agents, provides both a meaningful and easily accessible set of tumor cell properties on which to base a new dynamic characterization of glial tumor cells. Thus, the clinical chemotherapy agents become biological probes in the characterization process as well as objects of sensitivity/resistance testing.

At the heart of this approach to the glial tumor cell is the aqueous microcytotoxicity assay. This simple assay has provided a quick, reliable determination of chemotherapeutic agent sensitivity or resistance applicable to almost all human glioma lines available from the operating room. In addition, as shown in a retrospective clinical study in fourteen patients, it appears to have clinical predictive value, most reliably for resistance.

One limitation of the aqueous assay is the fact that certain agents one would like to test are of limited or no aqueous solubility. The use of organic solvents, even in low concentrations, can complicate the determination of cytotoxicity and thus may be undesirable. Accordingly, we have continued to develop an assay in which the drug to be tested is solubilized in a volatile organic solvent. The organic solvent is then evaporated, leaving the drug as a surface coat on the bottom of the well. The tumor cells to be evaluated are then plated on top of the drug and exposed for periods of up to 168 hours. In this case, the tumor cell membrane acts as the drug solvent and delivers the drug directly into the cytoplasm. For both BCNU and AZQ, which have limited aqueous solubility but can be tested in both the aqueous and solid-phase assay, the data indicate the solid-phase assay provides a comparable and equally reliable measure of glial tumor cell resistance or sensitivity.

Another limitation of the microcytotoxicity assay system, whether aqueous or solid-phase, is the time-consuming nature of the cell-counting process required for evaluation of sensitivity and/or resistance. For an experienced human observer, counting a single plate (48 wells) takes 40-60 minutes with another 30 minutes required for calculations of cytotoxic indices,

$$\left(\text{C.I.} = 1 - \frac{\#\ \text{cells test well}}{\#\ \text{cells control well}}\right)$$

standard deviations, and t-values. To solve this problem we have developed an automated, image-analysis based system permitting the processing of each plate, including statistical output within 15 minutes. The methodology developed should have a broad utility for both chemotherapeutic and immunologic assays using microtiter or other multiwell plates. It is worth adding that the automated image analysis system is capable of quantitative morphometry as well as simple counting so that it is possible to determine morphological changes resulting from drug or other treatment as well (i.e. change in area, perimeter, length-to-breadth ratio, maximum chord, etc.).

Since the image analysis system has also been interfaced to our scanning and transmission electron microscopes, this analysis can be extended to ultrastructural analysis of drug action and cellular response.

An adequate glioma cell characterization program is, of course, much more than the few elements mentioned above. Without going into further detail about other subcomponents, the following list is a summary of the elements as they are currently used in the SNB:

1. Aqueous and solid phase microtiter plate assays - Sensitivity - Resistance,
2. Antigenic expression and tumor cellular immune characteristics,
3. DNA alkaline elution assay; Interstrand cross-links; strand breaks,
4. DNA flow cytometry,
5. Bioelectrical properties,
6. Receptor analysis; protein kinase coupling,
7. Metabolic techniques aerobic, anaerobic metabolism,
8. Peptide protein synthesis release characterization,
9. Marker expression GFA, FN S-100 Factor VIII,
10. Scanning and transmission EM preps quantitative autoradiography,
11. Image analysis quantitative morphometry.

The following chemotherapeutic agents and/or other biological probes have been used thus far in the characterization program outlined above:

	Chemotherapy Agents:	Growth-regulatory or "Differentiation-Active" Biological Agents:
1.	Nitrosoureas	cAMP
	BCNU	cGMP
	PCNU	Dimethylformamide and other polar solvents
	HeCNU	
	CCNU	Interferon (glioma)
2.	AZQ	Interferon (fibroblast)
3.	Cis-platinum	Epidermal Growth Factor (EGF)
4.	Spirohydantoin	Fibroblast Growth Factor (FGF)
5.	Rapamycin	β-adrenergic agonists
		Butyrate
		Phenytoin
		A 23187
		5-azacytidine

This paradigm involves the individual as well as collaborative work of Drs. J. Bressler, B. Chronwall, C. Cummins, M. Gately, P. Kornblith, P. McKeever, N. Shitara and B. Smith.

The major findings of these studies over the past year include:

1) The variability of glioma cell lines as defined by their responses to chemotherapy agents is clear. This has been documented in approximately 150 human glioma-derived cell lines for BCNU, 60 such lines for AZQ and some thirty lines for cis-platinum in the microcytotoxicity assays. Thirteen lines have now been evaluated with the DNA alkaline elution assay in collaboration with Drs. Kurt Kohn and Len Erikson of the National Cancer Institute with good correspondence to the microcytotoxicity assay data. Not only do glioma-derived cell lines differ from each other with respect to sensitivity and resistance to any given agent, but there are relatively sensitive and resistant sub-populations within a single tumor-derived cell line.

2) Although there are relatively sensitive and resistant cells within a given glioma cell population, the level of population sensitivity as measured by the C.I. is a useful indicator of population properties and appears to correlate with clinical response. For the DNA alkaline elution assay, the number of interstrand cross-links and strand breaks appear to be similarly predictive.

3) The variability of response noted for the chemotherapy agents is also seen with the biological agents including cyclic AMP, dimethylformamide (DMF), glioma or fibroblast-derived interferon (GDIF, HFIF) and epidermal growth factor (EGF) and fibroblast growth factor (FGF). This variability is seen whether "response" is defined as quantitative morphological change or receptor coupling to protein kinase, interferon production, or growth kinetics and cytotoxic index.

4) It is possible to determine mechanisms of sensitivity and/or resistance to chemotherapy agents or their biological probes. Clearly established in the past year have been:

   a) The selective mitochondrial toxicity of AZQ;

   b) Independence of resistance to BCNU and platinum such that for a BCNU-resistant glioma cell, platinum provides a realistic therapeutic alternative;

   c) Sulfhydryls in tumor cells inhibit platinum's action and may represent part of the mechanism of resistance to platinum.

Neuropathological characterization has also continued and has been directed toward improving diagnosis of biopsies at surgery and characterizing the cells which are cultured from gliomas. The first of these

activities has coincided with the establishment of a diagnostic neuropathology service at the NIH Clinical Center by Dr. McKeever with the full assistance from and support of Drs. Kornblith, Rabson, Costa and Valsamis.

Fluorescence and peroxidase staining of frozen sections for glial fibrillary acidic protein (GFAP), fibronectin, carbohydrate containing stroma and pituitary granules has been successfully employed to improve diagnosis of gliomas, nonglial neoplasms and pituitary adenomas.

Proteins released from neoplasms outside of the central nervous system have provided diagnostic information about the neoplasms and biological information about their cells of origin. Therefore, primary attention was focused on the question of protein release by cells cultured from gliomas. Since these cells required serum for growth in vitro, a system was sought which would test for cellular synthesis and release of proteins in the presence of serum. Cells from human gliomas were exposed to radiolabeled amino acids and assays for protein synthesis and release. A number of previously unknown proteins designated P175, P125, P60, P47 and P40 for their particular molecular weights were found to be released. Specific inhibition of protein synthesis with cycloheximide showed that the released proteins had been synthesized by the cells. Prototype mammalian gliomas also released a number of proteins. The possibility that one or more of the proteins are responsible for the lymphocyte suppression by gliomas (see Immunology section) is of great interest and being pursued.

In order to locate and identify cells on an individual basis, a marker for astrocytes was borrowed from Surgical Neuropathology. Immunofluorescence for GFAP had been developed and used on biopsy material. Double immunofluorescence for anti-glial fibrillary acidic protein (anti-GFAP) and for fibronectin was being used to distinguish glial from non-glial neoplasms on frozen sections with clear-cut results. Of particular relevance in astrocytomas, the neoplastic glial cells contained GFAP and not fibronectin while divergent cells, in particular the paraneoplastic cells which contribute to vascular and vessel wall proliferation contained fibronectin and not GFAP. Sterile astrocytomas from surgery were followed with markers for GFAP and fibronectin through the process of frozen sectioning of whole tumor, mincing, explanting and passing into culture. At initial explantation, cells containing only GFAP grew from certain fragments of tumor while cells containing only fibronectin grew from other fragments. This phenomenon would not have been noticed without examination of initial explants, since the cells become thoroughly mixed upon initial passage. It was thus possible to separate known glial cells from divergent cells upon explantation.

Electron microscopic studies have revealed differences between the two immunologically defined cellular subpopulations cultured from gliomas. Glial cells seem to have more intermediate filaments, while divergent cells appear to have more extracellular filaments and more swollen endoplasmic reticulum. Scanning electron microscopy demonstrated the known glial cells to have more and thinner processes than the divergent cells. These morphologic impressions are being quantitated by computerized

morphometry. Work on the localization of S-100 and Factor VIII (an endothelial cell marker) is also in process.

Metabolic characterization studies have also been conducted over the past year. The major research effort in this area has been to elucidate the unique features of the energy metabolism of glial tumors. The rates of glucose consumption in glia-derived tumor cell lines measured *in vitro* appear close to the CMR_{glc} of the tumor *in situ*, measured by PET scanning techniques. This lends credence to the use of glioma-derived cell lines as a reasonable model system for gliomas *in situ*. Also being evaluated in these studies are the utilization of carbon sources other than glucose (i.e., glutamate and glutamine) in malignant glial cells. On the basis of the rates of uptake, and the number of moles of ATP potentially generated from each mole of glutamate or glutamine, these amino acids from our studies may be a more significant energy source than glucose. Finally, tumor cell hexokinase as a regulator of glycolysis is being studied. We have measured the affinity (Km) for the constant carbohydrate substrate and the maximal catalytic activity (V max) from a variety of glioma-derived and fibroblast (control) cell lines. The kinetic constants are close to those reported for other mammalian brain enzymes.

Overall, then, the characterization program is moving ahead on several fronts and the complex matrix of malignant brain tumor properties being unravelled. Progress is gratifying in this area.

B. Chemotherapy

The basis for the clinical protocol progress in chemotherapy that has been achieved in the SNB has been the application of *in vitro* microcytotoxicity testing, i.e., the testing of individual patient tumor lines with a series of chemotherapy agents to determine which may be most effective for a given tumor. Such studies, together with other characterization efforts, have indicated the diversity of properties of malignant glial tumors. Given the same pathological diagnosis for a group of these tumors, a wide range of biological properties and, consequently, therapeutic sensitivities are found.

Utilizing the aqueous *in vitro* chemotherapy sensitivity assay developed by Dr. Kornblith and the solid-phase assay developed by Dr. Smith, populations of glial tumor cells either sensitive or resistant to the nitrosourea, BCNU, and several other anticancer drugs including AZQ, cis-platinum, CBDCA, Henkel compound, rapamycin and spirohydantoin have been determined. The basis of resistance to BCNU of glial tumor cells, based on collaborative studies with Drs. Kurt Kohn and Len Erikson of the National Cancer Institute, is the ability of the tumor cell to repair DNA damage resulting from drug-induced interstrand cross-links and strand breaks. In addition, we have determined that different cell membrane and microsomal protein properties (i.e., p 450) in sensitive and resistant cell populations also play a role in BCNU's effectiveness in tumor cell killing. The knowledge of such differences as they relate to the mechanisms of actions of various drugs has thus led not only to an appreciation of the importance of

individualized glioma patient chemotherapy but also directly to the clinical protocols described above. In addition, the microcytotoxicity assay-derived sensitivity and mechanism data are suggesting ways to modify or circumvent tumor cell resistance mechanisms, thereby making it possible to begin to attempt to convert resistant cells into drug-sensitive cells.

The in vitro assays utilized have, for example, suggested the usefulness of both AZQ and cis-platinum (or derivatives thereof) for malignant glioma therapy. AZQ has been of particular interest because of:

a) Its demonstrated effectiveness in our in vitro microcytotoxicity assay,

b) Its high central nervous system penetration,

c) Its apparent 10-fold concentration in glial tumors as opposed to plasma (as determined in our clinical studies),

d) Its selective mitochondrial destruction as well as nuclear DNA interstrand cross-linking,

e) Its relatively minimal side effects as seen in our Phase I studies.

Although BCNU, AZQ and cis-platinum all attack DNA, we have determined that they are not limited by the same mechanisms of resistance. Thus, AZQ and cis-platinum are rationally-based therapeutic alternatives to BCNU.

Based on SNB studies of AZQ in 20 patients (with recurrent malignant gliomas and failure to respond to radiation therapy and other chemotherapy), we have achieved a 25% response rate as demonstrated by clinical and CT scan improvement. Mean duration of response is approximately four months to date. Patients have been carried on this drug (monthly cycles) for up to 9 months. Our data parallel that of the Mayo Clinic and the M.D. Anderson Hospital.

Progress in this area has been such that it is now possible to think in practical terms about an individualized attack on each glioma patient's tumor. This progress has lead to a new SNB protocol designed to prospectively plan optimal chemotherapy for each patient based on three in vitro assay modes - aqueous microcytotoxicity testing, solid phase microcytotoxicity testing, and an alkaline elution DNA assay.

The in vitro assays are also being utilized to develop promising new antiglioma agents, both of the traditional chemotherapy agent type as well as the newer biological growth control or "differentiation" agents such as dimethylformamide (DMF) and the various subtypes of interferon. Basic studies underway in these areas should be productive of new SNB clinical protocols. A major new protocol "The Prospective In Vitro Selection of Chemotherapy Agents for Patients with Malignant Brain Tumors" is now being implemented as the natural outgrowth of the basic studies.

A significant event in the SNB laboratory relevant to both chemotherapy and immunological microcytotoxicity testing has been the design and development of an automated image analysis system for the quantitation of not only cell number but also morphometric characteristics of treated glioma cells by Dr. Smith in collaboration with the Biological Engineering and Instrumentation Branch of the NIH, Division of Research Service. The time to process the microtiter plates and produce accurate, statistically analyzed results has been reduced from 90 to 15 minutes per plate. The availability of this system has significantly increased our capability for both basic and clinical evaluation of central nervous system tumor cell biological properties and the responses of such cells to chemotherapeutic, immunological and biological modifying agents. Its availability is critical to the type of prospective clinical chemotherapy agent selection trial described above.

C. Immunology

Work has proceeded in both humoral and cellular immunology. In the serological response studies the correlation of serological immune response with malignancy and glioma patient survival has been evaluated. These studies of glioma patients' circulating antiglioma antibody tested against their own tumor cells in culture have shown diminishing effectiveness with increasing malignancy of the tumor. In general, high levels of antibody are found in younger patients and correlate with increased survival. Thus, these immune assays have prognostic value -- a first for glioma studies.

In the past year we have determined that it is possible to modify tumor cell susceptibility to antibody-induced, complement-mediated cytolysis. Treatment of malignant glial tumor cells in vitro with either dibutryl cyclic AMP or DMF has resulted in the conversion of antibody-resistant glioma cells to sensitive cells. Work is currently in progress to determine the reason for this change. Altered antigenic expression is a leading possibility.

In studies of tumor defenses against host cellular immunity mechanisms, we have previously demonstrated three mechanisms by which human gliomas may escape cellular immune attack: (1) a defect in immunogenicity which can be overcome by "help" from an allogeneic mixed lymphocyte reaction (MLR), (2) the secretion of mucopolysaccharide cell coats, and (3) the production of a macromolecular immunosuppressive substance. Work during the past year has been directed at further understanding how these mechanisms operate. Major new findings include the following. "Help" provided by MLR in facilitating cytolytic lymphocyte responses to glioma-associated antigens is due to the action of soluble factors released by lymphocytes during the course of the MLR. Likewise, the secretion of large mucopolysaccharide cell coats by glioma cells is due to the interaction of the glioma cells with a soluble macromolecular factor(s) produced by some component of the blood mononuclear cell population. In the absence of blood mononuclear cells or supernatants from cultures of blood mononuclear cells, only thin mucopolysaccharide coats are made by the glioma cells.

The immunosuppressive substance released by glioma cells was found to elute from a gel filtration column in the same fractions as marker proteins of 60,000 - 80,000 molecular weight. The factor recovered from the column inhibited mitogen responses as well as the generation of cytolytic lymphocytes in mixed lymphocyte cultures.

A clinical immunological protocol designed to evaluate the effects of peripherally injected, irradiated autologous tumor cells on patient cellular and humoral immune status has been in progress for two years. Data in three patients so treated indicate no toxicity but no significant immune effects of such treatment. Clearly, if immunological therapy of this and other types (such as tumor-specific, monoclonal antibody) are to be successful, both tumor and host immune defense mechanisms and weaknesses will have to be understood. Current progress in the SNB makes practical advances in this area look likely in the near future.

D. Brain Tumor - Coagulation System Interactions

Alterations of hemostasis in cancer patients have long been recognized, and continue to be the subject of extensive research. Thrombolic and/or hemorrhagic complications have been reported with almost any type of cancer but are thought to be more common in carcinoma of the pancreas, lung, stomach and ovary. Brain tumors, on the other hand, have not been evaluated in any systematic way; however, existing information namely, blood clotting changes, increased platelet stickiness, and induction of thrombosis in animals with extracts of glial tumors coupled with our observation of the frequent occurrence of thrombo-embolic complications, indicate that hemostatic disorders probably occur with a certain frequency and represent a real threat to the survival of our patients.

In order to elucidate the frequency, pathogenetic mechanisms and significance of such complications, this year we have established, under the direction of Dr. R. Sawaya, a program combining clinical and laboratory research. The clinical program includes a complete historical and physical evaluation of our patients, pre- and postoperatively, in a combination with detailed nursing assessment and I^{125}-fibrinogen scanning prospectively in our attempts to determine the incidence of thrombotic phenomena and to identify the risk factors particular to our patient populations. Basic hematological assessment is also included and correlated with clinical and scanning data.

The laboratory program evaluates the thromboplastic and fibrinolytic potential of gross tumor explants freshly obtained from the operating room and of tissue culture explants obtained from our tissue culture laboratory.

E. PET Scanning

Another area of significant accomplishment for the Branch has been the development of a positron emission tomographic scan capability by the section of Neuroradiology and Computed Tomography under Drs. G. Di Chiro

and R. Brooks. Two major facets of this program have included: 1) study of ^{18}F-2-deoxyglucose tumor metabolism in some 70 glioma patients over the past two years; 2) the development, building and operation of a new SNB-designed high resolution PET Scanner - the NEUROPET - designed for the central nervous system and offering a resolution three-fold better than that available in state-of-the-art commercially produced equipment.

PET studies in the 70 glioma patients studied to date have shown a correlation of malignancy and tumor metabolism -- the more malignant the tumor, the higher its metabolic rate. Parallel in vitro studies of glioma cell metabolism carried out by Dr. Craig Cummins have helped to validate this correlation. Not only improved "non-invasive" tumor grading but also earlier detection of recurrence and thus improved patient follow-up have all been achieved thus far. With the new higher resolution NEUROPET, the availability of glioma-specific monoclonal antibody, and an expanding positron-emitter labelling capability for a variety of metabolic substrates and other markers, rapid progress in this area seems possible. More details are given in the section on Neurodiagnostic Studies.

F. Animal Model (RT9) Tumor Studies for Evaluation of Tumor Blood Flow, Blood-Tumor Transport and Drug Delivery

The RT9 glial tumor has been studied after intracranial implantation in rats with respect to blood flow, blood-to-brain transport, and drug delivery in collaboration with Drs. J. Fenstermacher and R. Blasberg of the NCI. Using radiolabelled iodoantipyrene (IAP) amino-isobutyric acid (AIB), and misonidazole, these studies involving both scintillation counting techniques as well as quantitative autoradiography have demonstrated:

1) Heterogeneity of blood flow with a given intracranial RT9 tumor with flow not necessarily correlated with histology;

2) Depression of blood flow to the entire tumor-containing hemisphere;

3) Variability within regions of a given tumor of blood-to-brain transport with no necessary correlation with flow or histology but an overall increase of such transport in tumor as compared to normal brain of up to 26-fold;

4) Variability in misonidazole delivery without necessary correlation to blood flow or histology.

These facts are important for understanding the complexity of tumor organization,especially as it relates to drug delivery.

2. BIOLOGICAL STUDIES OF HUMAN PITUITARY TUMORS

The secretion of hormones by normal and neoplastic anterior pituitary cells has been an ongoing effort of this laboratory for several years. As noted in the previous report, a surprising finding has been that certain pituitary tumor cells in tissue culture secrete not only the hormone which they have classically been known to produce clinically but also a range of other hormones.

Efforts have continued to include:

1) Improvement in the diagnostic classification of pituitary tumors;

2) Regulation of hormone secretion as phenotypic expression in neoplastic pituitary cells;

3) Mechanisms and regulation of secretion of pituitary hormones.

A major problem in this area continues to be the fall-off in hormone production over time in most lines. Continued searching for stable lines is an important element of this project area. We continue to obtain secreted hormone profiles over periods of time, ranging from 1 week to several months. Hormones in the assay have included ACTH, GH, PR2, L21, and FSH. CRF is also being examined in intact animal models.

3. NEURODIAGNOSTIC STUDIES INCLUDING THE PET SCAN RESEARCH IN THE NEURORADIOLOGY AND COMPUTED TOMOGRAPHY SECTION

The bulk of the research efforts of this section have concentrated on Positron Emission Tomography (PET).

Positron Emission Tomography (PET) using [^{18}F] fluorodeoxyglucose (FDG), represents a totally new approach to the understanding of the pathophysiology of many neurological diseases. This method provides physiological information not available with any other imaging procedure.

During the past year we have:

1) Obtained and analyzed data with the FDG-PET technique in a large number of patients (over 70 cases at the last count) harboring cerebral tumors. These data clearly indicate that the FDG-PET technique is a powerful research tool to obtain information on some metabolic features of the new diagnostic and basic insights about these lesions;

2) Completed the construction of the NEURO-PET, a new high resolution-high sensitivity PET tomograph. This device has already been tested successfully in patients;

3) Provided the indispensable theoretical and technical expertise for FDG-PET project by other NINCDS branches. These projects deal with epilepsy, Alzheimer's disease, dyskinesias, Parkinson's disease and ALS.

The Neuroradiology and Computed Tomography Section is also involved in the following other research projects:

Transmission Computed Tomography (CT). Our work involves continuing clinical-animal/experimental research projects. These include studies of demyelinating, degenerative and atrophic processes of the brain, brain edema, hydrocephalus, postradiation cerebral necrosis, diseases of the spine and the spinal cord, surgically correctable lesions in young patients affected by chronic epilepsy, attempts at tissue characterization of normal and tumoral cerebral tissue, and an experimental glioma model in primates.

Selective Arteriography of the spinal cord is a diagnostic technique which has been most informative in cases of tumor, arteriovenous malformation, trauma, obstructive vascular disease, and postradiation damage of the spinal cord.

Radioisotope angiography of the spinal cord offers distinct advantages as a method of screening, and may give information not available by any other diagnostic test in certain kinds of intraspinal pathology.

Our experience with dynamic computed tomography (DCT) of the spine after injection of contrast medium shows that this methodology is helpful in the evaluation of certain vascular lesions of the spinal cord.

Our preliminary digital subtraction angiography (DSA) studies of the spine in cases of arteriovenous malformation and tumors of the spinal cord have been very successful. DSA is a valuable screening and follow-up technique for the evaluation of certain vascular conditions of the spinal cord.

4. NEUROPHYSIOLOGICAL STUDIES

Under the direction of Dr. Choh-Luh Li, investigations of the neurophysiological mechanisms of pain have been carried out. Over the course of the year Dr. Chang Hsiang-Tung of the Peoples Republic of China has continued to collaborate in the research. Emphasis has continued to be on pain mechanisms using the cat vagus nerve model. The left vagus nerve and right sural nerve are utilized and brain stem recordings have been made in the ganglion nodosum, nucleus tractus solitarius and nucleus parafascicularis. We have determined that there are direct connections of the A-delta and C-fibers with the ganglion nodosum and that this transmission is not affected by morphine. In the nucleus tractus solitarius, neuronal activiation is also by vagal input (C or A-delta). Metabolic studies of this activation as well as of activity patterns in the nucleus parafascicularis and nucleus centralis lateralis continue.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER ZO1 NS 02367-04-SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biological, Immunological and Chemotherapeutic Studies of Human Brain Tumors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Paul L. Kornblith	Chief	SN NINCDS
OTHER:	Barry H. Smith	Deputy Chief	SN NINCDS
	Maurice K. Gately	Senior Staff Fellow	SN NINCDS
	Paul E. McKeever	Medical Officer	SN NINCDS
	Nobuyuki Shitara	Visiting Scientist	SN NINCDS
	Bibie Chronwall	Visiting Fellow	SN NINCDS
	Craig Cummins	Staff Fellow	SN NINCDS
	Yoshio Moriya	Visiting Fellow	SN NINCDS
	Joseph Bressler	Senior Staff Fellow	SN NINCDS
	Raymond Sawaya	Visiting Scientist	SN NINCDS
	Conrad Kufta	Senior Staff Fellow	SN NINCDS
	Edward Oldfield	Senior Staff Fellow	SN NINCDS

COOPERATING UNITS (if any) Radiation Oncology, NCI; Medical Oncology, NCI: BEIB, DRS, NIH

LAB/BRANCH
Surgical Neurology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5.0	4.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Human brain tumors are evaluated in a tissue culture environment as to their basic biological behavior, their response to chemotherapeutic agents and the detailed immunological interactions between the host and the tumor. A primary goal is to improve the therapy of patients by understanding the basic cellular biology of malignant human brain tumors.

SNB has continued the biological characterization program with the inclusion of flow cytometry, karyotyping, glial fibrillary acid protein, fibronectin, S-100 and Factor VIII assays, DNA repair, adrenergic and other receptor assays, ganglioside and glycoprotien assays, cloning techniques, in-depth neuropathological studies, and automatic image analysis; utilized both aqueous and surface chemotherapy assays to test several new potential antiglioma agents and initiated a prospective in vitro selection of clinical trials with these agents; carried out protocols with AZQ and platinum derivatives; defined the basis of cellular sensitivity or resistance to nitrosoureas; characterized the humoral cellular immunological response to gliomas; and carried out correlative cellular and PET scan glucose metabolic studies.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02368-04 SN

PERIOD COVERED
October 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biological and Immunological Factors in Peripheral Nerve Regeneration

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Barry H. Smith	Deputy Chief	SN	NINCDS
	Paul L. Kornblith	Chief	SN	NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
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SECTION
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NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The studies were designed to determine factors contributing to failure of peripheral nerve regeneration in animals and humans. A rat model for study of these factors was developed successfully and several factors defined.

The study has been discontinued for the present due to lack of scientific personnel to work in this area.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02454-02-SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biological Studies of Human Pituitary Tumors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Edward H. Oldfield	Senior Staff Fellow	SN	NINCDS
Other:	Barry H. Smith	Deputy Chief	SN	NINCDS
	Paul E. McKeever	Medical Officer	SN	NINCDS
	Paul L. Kornblith	Chief	SN	NINCDS
	Craig Cummins	Staff Fellow	SN	NINCDS

COOPERATING UNITS (if any)

Department of Neurosurgery, Georgetown University

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Surgical Neurology Branch

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pituitary tumor cells in tissue culture have been determined in this laboratory to produce not only the hormones which they have been classically known to produce but also a range of one to several other hormones. The purpose of this study is to explore the mechanisms which control the production of hormones by these tumor cells in an effort to improve pathological classification and diagnosis, accuracy of prognosis, prediction of recurrence, and ultimately therapeutic approaches. Cushing's disease is of special interest in this regard.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01047-20 SN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Radionuclide Ventriculography and Cisternography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Di Chiro	Chief, Neuroradiology and Computed Tomography Section	SN NINCDS
OTHER:	G.S. Johnston	Chief, Nuclear Medicine Dept.	NM CC
	A.E. Jones	Assistant Chief	NM CC
	R.A. Brooks	Staff Physicist	SN NINCDS

COOPERATING UNITS (if any)

Nuclear Medicine, Clinical Center, NIH

LAB/BRANCH

Surgical Neurology Branch

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Neuroradiology and Computed Tomography Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Radionuclide ventriculography and cisternography are diagnostic tools permitting the morphologic and dynamic study of the cerebrospinal fluid pathways more accurately than has even been possible with any other diagnostic test.

This project has been discontinued.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01195-18 SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Radiographic and Radioisotopic Angiography of the Spinal Cord

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Di Chiro	Chief, Neuroradiology and Computed Tomography Section	SN NINCDS
OTHER:	J.L. Doppman	Chief	DR CC
	K.G. Reith	Staff Radiologist	DR CC
	P.L. Kornblith	Chief	SN NINCDS
	E.H. Oldfield	Senior Staff Physician	SN NINCDS
	A.E. Jones	Acting Chief	NM CC
	A.L. Tievsky	Staff Fellow	Geo.Wash.Univ.
	D.O. Davis	Chairman, Dept. of Radiology	Geo.Wash.Univ.

COOPERATING UNITS (if any) Diagnostic Radiology and Nuclear Medicine Departments, Clinical Center, NIH; Department of Radiology, George Washington University Medical School, Washington, DC; Medical Examiner's Office, Department of Public Health, Philadelphia, PA

LAB/BRANCH
Surgical Neurology Branch

SECTION
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NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.166	0.166	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Selective arteriography (radiographic) of the spinal cord is a diagnostic technique which has proven to be very informative in cases of arteriovenous malformation, tumor, obstructive vascular disease, trauma, and postradiation damage of the spinal cord.

Radioisotope angiography of the spinal cord offers distinct advantages as a screening method, and in certain types of intraspinal pathology may give information not available by any other diagnostic test.

Preliminary experience with two new techniques, dynamic computed tomography (DCT) and digital subtraction angiography (DSA) of the spine indicate that these methods are useful, and indeed excellent screening and follow-up procedures in the evaluation of certain vascular lesions of the spinal cord.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 01654-15 SN

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Experimental Spinal Cord Angiography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Chief, Neuroradiology and Computed Tomography Section	SN NINCDS
OTHER:	P.L. Kornblith	Chief	SN NINCDS
	B.H. Smith	Deputy Chief	SN NINCDS

COOPERATING UNITS (if any) J. Fein, Department of Neurological Surgery, Albert Einstein College of Medicine, Bronx, NY, formerly of Armed Forces Radiobiology Research Institute, Bethesda, MD; K. Earle, Chairman, American Registry of Pathologists, Washington DC

LAB/BRANCH
Surgical Neurology Branch

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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental spinal cord angiography in the rhesus monkey is increasing our understanding of the blood supply of the spinal cord both in physiological and pathological conditions.

This project has been discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02073-09 SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Computed Tomography (Transmission) and Nuclear Magnetic Resonance (NMR)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Di Chiro	Chief, Neuroradiology and Computed Tomography Section	SN NINCDS
	R.A. Brooks	Staff Physicist	SN NINCDS
	K.G. Rieth	Staff Radiologist	DR CC
	V.J. Sank	Expert	
OTHER:	P.L. Kornblith	Chief	SN NINCDS
	B.H. Smith	Deputy Chief	SN NINCDS
	A.M. Cormack	Physicist	Tufts University
	J.L. Sever	Chief	ID NINCDS
	W.T. London	Chief, Experimental Pathology Section	ID NINCDS

COOPERATING UNITS (if any) Diagnostic Radiology, Nuclear Medicine Department, CC, NIH; Infectious Diseases Branch, IRP, NINCDS, NIH; Physics Department, Tufts University, Medford, MA.

LAB/BRANCH
Surgical Neurology Branch

SECTION
Neuroradiology and Computed Tomography Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.333	0.333	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computed Tomography (CT) in its transmission, emission and soon NMR modalities, represents the main research area of the Neuroradiology & Computed Tomography Section.

Ongoing clinical - animal/experimental research projects in transmission CT include studies of degenerative, demyelinating and atrophic processes of the brain, hydrocephalus, brain edema, postradiation cerebral necrosis, surgically correctable lesions in young patients affected by chronic epilepsy, diseases of the spine and the spinal cord, attempts at tissue characterization of normal and abnormal (e.g. tumoral) cerebral tissue, and an experimental glioma model in primates.

Physics projects: improved dual-energy CT scanning using both a split-detector and a dual kVp method; analysis of aliasing effects and development of methods for their elimination; phantom studies for the evaluation of artifacts and calibration of CT machines; feasibility tests for a new type of CT device which will use protons instead of x-rays.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02315-05 SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Positron Emission Tomography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Di Chiro	Chief, Neurorad. & Comp. Tomog. Section	SN NINCDS
	R.A. Brooks	Staff Physicist	SN NINCDS
	V.J. Sank	Expert	SN NINCDS
	N.J. Patronas	Guest Staff Fellow	SN NINCDS
	P.L. Kornblith	Chief	SN NINCDS
	B.H. Smith	Deputy Chief	SN NINCDS
	R.J. Porter	Act'g Chief, CES (Also Chief, EB, NDP)	ET NINCDS
	M. E. Newmark	Neurologist	EB NINCDS
	T.N. Chase	Director	IRP NINCDS
	A.E. Jones	Acting Chief	NM CC
	R.M. Kessler	Staff Physician	NM CC
	R.G. Blasberg	Medical Officer	LCP NCI
	A.P. Wolf	Senior Chemist (*See below for "OTHER")	Brookhaven

COOPERATING UNITS (if any) BEIB, DRS, NIH; Naval Res. Lab., Washington, D. C.; Washington University, St. Louis, MO; Lab. of Cerebral Metabolism, NIMH, NIH; Brookhaven National Lab., Upton, NY; Div. of Nuclear Medicine, Dept. of Rad. Sci., UCLA, Los Angeles, CA; ODIR/IRP, EB/NDP, ETB/IRP, NINCDS, NIH; LCP, NCI, NIH.

LAB/BRANCH
Surgical Neurology Branch

SECTION
Neuroradiology and Computed Tomography Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	3.5	0

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☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less -

Positron Emission Tomography (PET) with (^{18}F)-fluorodeoxyglucose (FDG) allows us to obtain anatomical data (e.g., axial transverse or coronal images of the brain) as well as dynamic functional data (such as regional cerebral glucose consumption rate; measurements of the storage, degradation and turnover of tagged metabolites; follow-through of the movement of the CSF in the deep CSF intracranial cavities). The unique property of PET is that it provides physiologic information not available with any other imaging procedure.

During the last year the construction of a high-resolution high-sensitivity scanner for head and animal studies -- the Neuro-PET has been essentially completed. Patients have been studied using this new tomography. The obtained scans provide excellent, high resolution images of the brain.

- -

*OTHER:	L. Sokoloff	Chief	LCM NIMH
	D.E. Kuhl		UCLA
	M.E. Phelps		UCLA

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 NS 02010-10 SN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Neurophysiological Mechanisms of Pain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Choh-Luh Li	Medical Officer	SN NINCDS
OTHER:	Chang Hsiang-Tung (Director, Brain Research Institute, Shanghai, PRC)	Scholar-in-Residence	SN NINCDS
	Takekane Yamaguchi	Visiting Fellow	SN NINCDS

COOPERATING UNITS (if any) Brain Research Institute, Shanghai, PRC; Academia Sinica Hormone Research Laboratory, University of California School of Medicine, San Francisco, California; Laboratory of Cerebral Metabolism, NIMH

LAB/BRANCH
Surgical Neurology Branch

SECTION
Laboratory of Neurophysiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1	1	0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As generally accepted, the A-delta and C-fibers in the peripheral nerves are related to pain sensation. It has also been found that about 80% of the fibers in the vagus nerve are C-fibers presumably mediating the pain sensation from the visceral organs. In the present experiment the vagus nerve of the cat and of the rats are stimulated and extracellular and intracellular responses are recorded from the ganglion nodosum, nucleus tractus solitarius, dorsal nucleus of vagus, nucleus centralis lateralis and nucleus parafascicularis. In the same experiment, as the vagus nerve is stimulated, the sural nerve or saphenous nerve is also stimulated at different intervals in order to investigate the interaction of the impulses from somatosensory and autonomic nerves recorded from the various subcortical nuclei. Furthermore as the vagus nerve is repetitively stimulated, changes in metabolism of the various nuclear structures were studied. The latter is performed in collaboration with Dr. Louis Sokoloff of the NIMH.

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